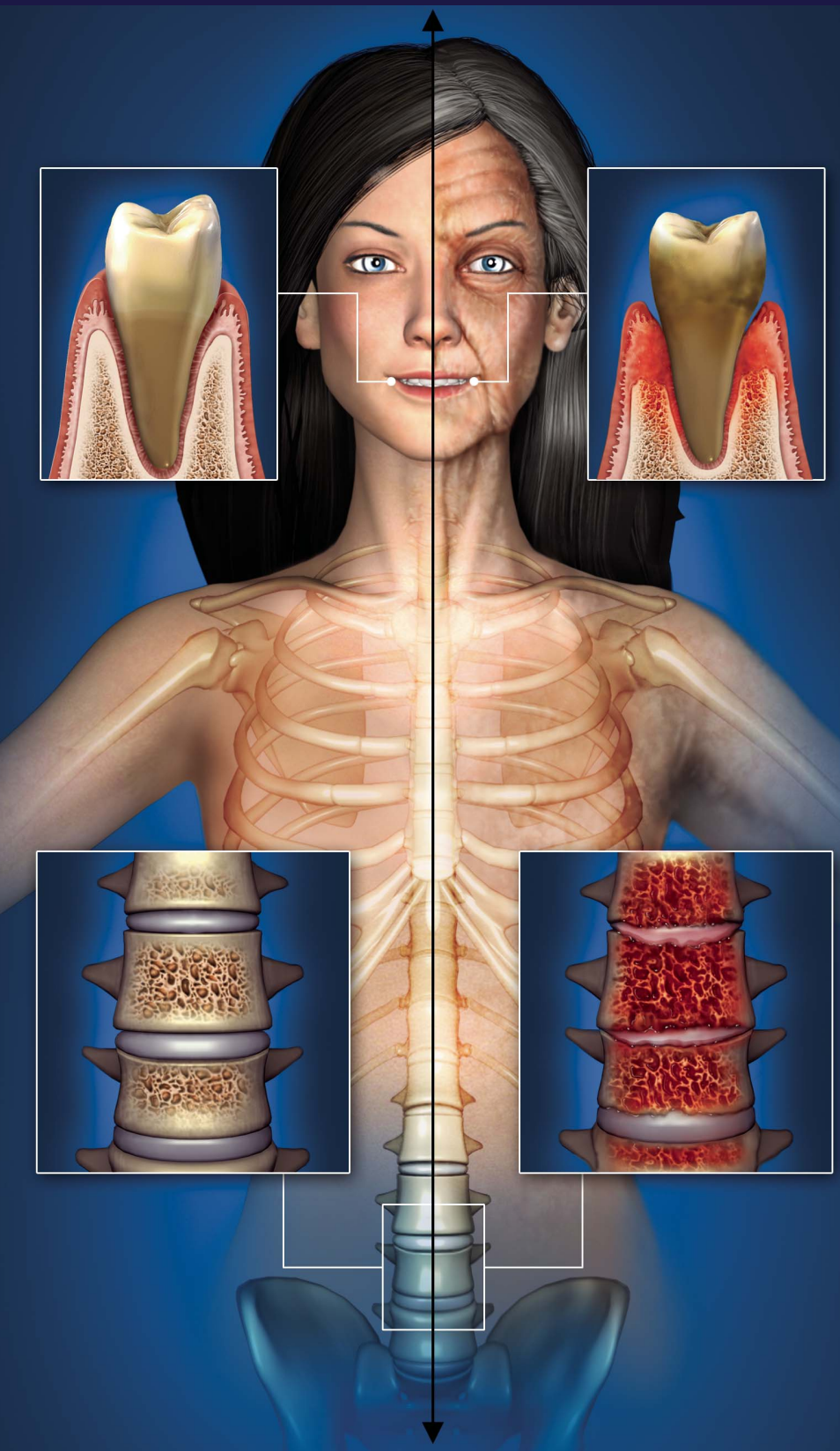
GRAND ROUNDS
in Oral-Systemic Medicine™

A Peer-Reviewed Journal

PennWell

May 2007, Vol. 2, No. 2



The Interrelationship between Osteoporosis and Oral Bone Loss

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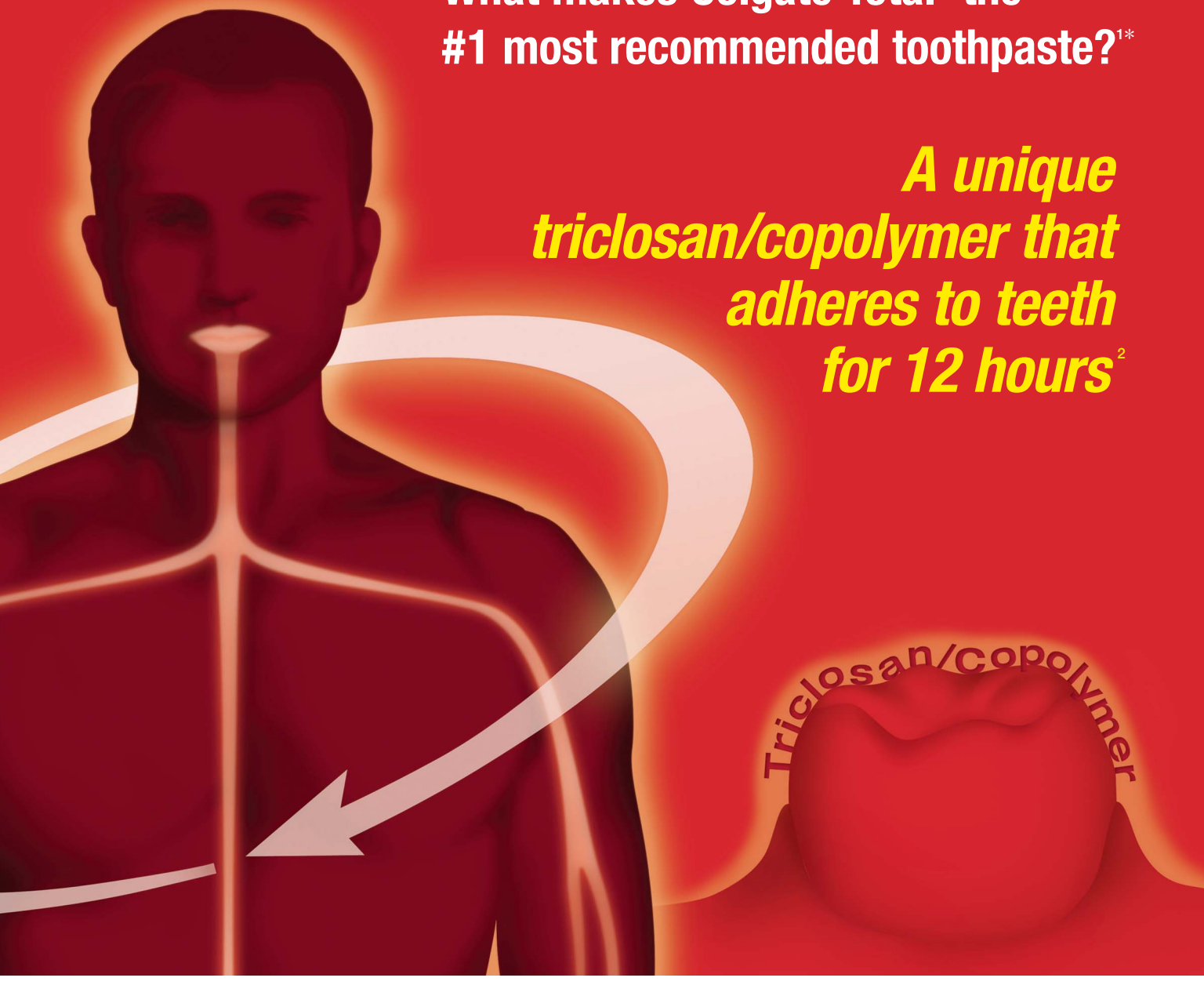

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1. Data on file. Colgate-Palmolive, New York, NY. **2.** Panagakos FS, et al. *J Clin Dent.* 2005;16(suppl):S1-S19.

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GRAND ROUNDS
in Oral-Systemic Medicine™
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Statement of Editorial Purpose: The editorial purpose of *Grand Rounds in Oral-Systemic Medicine*™ is to raise awareness of the importance of the relationship between oral and systemic health, and advance the understanding of oral-systemic science and its appropriate integration into the clinical practice of mainstream dentistry and medicine by providing editorial that:

- Compels members of the dental and medical communities to embrace the growing body of science called oral-systemic medicine and accept the uncertainty of its ongoing evolution.
- Translates/transfers credible and relevant scientific findings and scholarly thought related to oral-systemic medicine into authoritative editorial that is educational and engages all sectors of the healthcare professions (i.e., physicians and nurses, dentists and hygienists and allied healthcare providers).
- Stimulates collaboration and innovative thinking on how to transcend professional boundaries to integrate clinical protocols that include application of oral-systemic medicine in everyday patient care.

Policy on Submission of Manuscripts: The opportunity to contribute to the editorial mission of *Grand Rounds in Oral-Systemic Medicine*™ is offered to author candidates by honorary invitation. As such, unsolicited manuscripts are generally not accepted. Manuscripts published in *Grand Rounds in Oral-Systemic Medicine*™ are written by authors who are invited to contribute to this body of knowledge based upon their academic, research or clinical expertise, from both dentistry and medicine, in specific subject matters that pertain to oral-systemic medicine.

Staff

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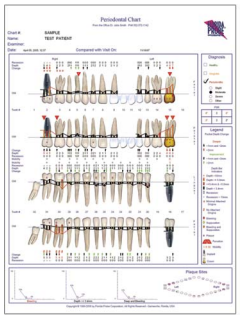

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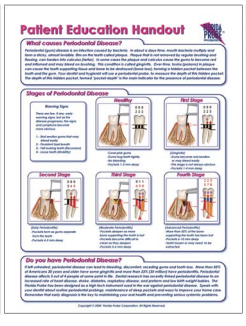

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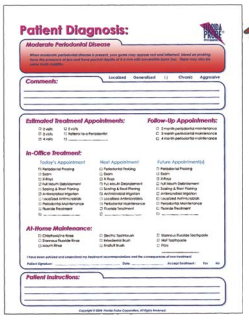

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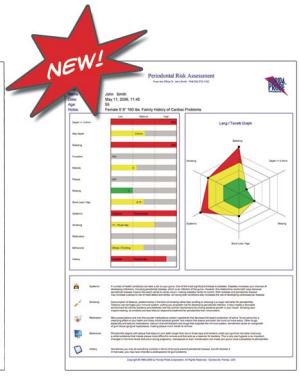

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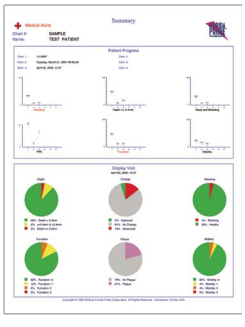

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GRAND ROUNDS
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IMPACTING OSTEOPOROSIS THROUGH MEDICAL-DENTAL COLLABORATION


Casey Hein


Tony Iacopino

This issue of *Grand Rounds* brings together some of the most knowledgeable and insightful experts on the subject of osteoporosis and its association to oral bone loss. As members of the baby boomer population grow older, many mature with a multitude of interrelated and life threatening chronic conditions, including osteoporosis — a disease with ravaging consequences. We believe it is time to bring osteoporosis and its association to oral bone loss to the forefront of dentistry and medicine. Dental and medical providers' willingness to move beyond "silo" thinking in the treatment of patients who are either at risk for or who are already diagnosed with osteoporosis has the potential to impact, on an individual basis, the trajectory of this disease.

In their comprehensive review of the literature, Drs. Giannobile, Ho, and Bashutski articulately point out that in the U.S., approximately 1.5 million of the fractures that occur every year are attributed to osteoporosis and that the number of people aged 50 or more with osteoporosis is expected to increase to 12 million by 2010 and 14 million by 2020. With these dismal statistics also comes the opportunity to impact the severity of both osteoporosis and periodontal disease by shifting from provider-centered "compliance" approaches to more patient-centered "empowerment" approaches in the care of patients at risk or diagnosed with osteoporosis. Consider the potential of medical-dental cross education of patients and reinforcement of the importance of oral health. For those readers who are seeking new models of care, Horn and Iacopino discuss transdisciplinary models of care that rely on dental hygienist-nurse collaboration as part of a comprehensive healthcare team in screening and treatment for osteoporosis.

There are a number of closely related oral-systemic relationships which merit discussion, and we are honored to have such distinguished researchers, academicians and clinicians from both medicine and dentistry weigh in on these subject matters. Two periodontists (Callan & Cobb) have teamed up with an orthopedic surgeon (Evans) to present a compelling hypothesis that bacteremia associated with periodontal disease may be associated with increased risk for failure of orthopedic joint replacements. An oral surgeon (Wade) and periodontist (Suzuki) contribute an up-to-date synopsis of the complexity of diagnosis and treatment planning associated with bisphosphonate-induced osteonecrosis of the jaws (BIONJ). In his new column dedicated to "Oral Pathology-Systemic Symposia", Sciubba presents a case involving an infection in an immunocompromised patient which ends in a fatal outcome — a powerful example of what happens when compromised patients are not properly evaluated for potential systemic consequences prior to surgery. "Front Line Perspectives" is hosted by dental hygienist, Fiacchi-Hudak, who has contributed a chilling story about a patient undergoing treatment for cancer who presented with BIONJ that was alarmingly overlooked by the patient's physician. Dr. Stuart Lieberman succinctly articulates CIGNA's plans to integrate care between its dental and medical programs aimed at improving outcomes and reducing costs associated with high-risk medical conditions. We are very honored to have Dr. E. Michael Lewiecki as our guest editor of this issue. His contribution provides an insightful and well-balanced perspective on how the medical profession views these at-risk patients. To Dr. Will Giannobile, thank you very much for the important role you played as the academic anchor of this issue of *Grand Rounds*.

Our hope is that our readers will champion this important message across disciplinary boundaries. We look forward to hearing from dental and medical providers alike on how this important information is translated into everyday patient care.

Sincerely yours,

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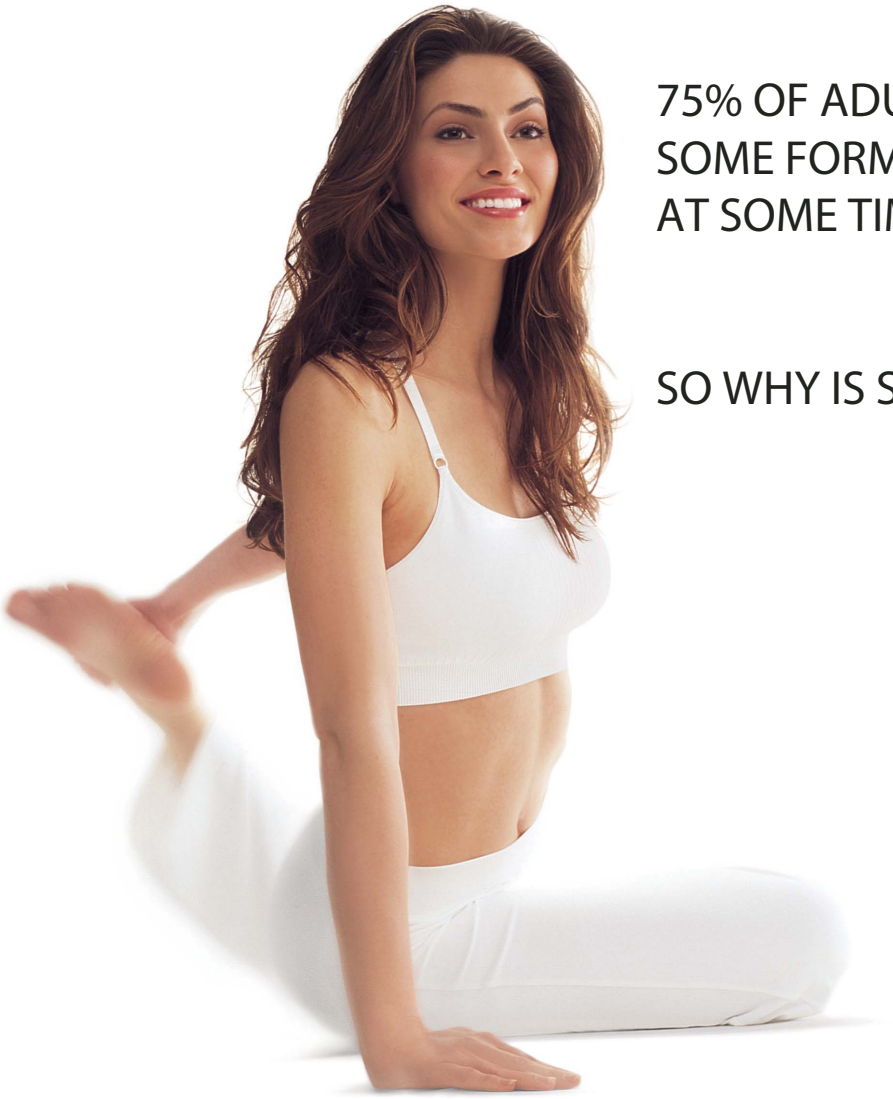

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1. ADA News Release, American Dental Association, September, 2001

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GRAND ROUNDS
in Oral-Systemic Medicine™

E. Michael Lewiecki, MD, FACP, New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM

GRAND ROUNDS WITH DR. MICHAEL LEWIECKI

Is there an association between osteoporosis and oral bone health, and if so, what is its nature and what are the clinical implications? This compound question broadly addresses a theme that is raised in this issue of *Grand Rounds in Oral-Systemic Medicine*.™ Osteoporosis is a systemic skeletal disease characterized by reduced bone strength and increased risk of low-trauma fracture. Periodontitis is a process characterized by alveolar bone loss and loss of soft tissue attachment to the tooth, leading to increased risk of tooth loosening and tooth loss. Osteoporosis and periodontitis share common risk factors that include advanced age, estrogen deficiency, cigarette smoking, glucocorticoid therapy, and anticonvulsant therapy. Both are silent diseases with serious clinical consequences. The "final endpoint" of fracture with osteoporosis and tooth loss with periodontitis is analogous in some ways to stroke in patients with hypertension and myocardial infarction in those with hypercholesterolemia. All of these underlying diseases are multifactorial in origin. The risk of their final endpoints can be reduced by appropriate medical interventions. It is plausible to hypothesize that osteoporosis, being a systemic disease, might have harmful effects on jaw bone, just as it does at other skeletal sites, and that this might be a contributing factor in the pathogenesis of periodontitis. It is also plausible to hypothesize that the inflammatory process initiated by bacterial infection and release of cytokines associated with periodontitis may have effects on bone both locally and systemically. There are other chronic inflammatory diseases that are associated with local and systemic skeletal effects. For example, rheumatoid arthritis (RA) is associated with focal bone erosions in areas of active arthritis as well as bone loss at skeletal sites that are remote from areas of active arthritis. Although the chronic inflammation of RA is autoimmune in origin, while the inflammation of periodontitis is because of bacterial infection, data[1] suggesting a relationship between these two disabling diseases support the concept of chronic inflammation having adverse skeletal effects.

Many studies have examined the relationship between osteoporosis and oral bone loss.[2] Most, but not all of these, have concluded that there is, or may be, a link between these disorders. Unfortunately, evaluation of the evidence is often confounded by small sample size, cross-sectional study design, inadequate control of variables, variable methods for assessing systemic bone mineral density (BMD) at different skeletal sites, and variable methods for measuring oral BMD. The "gold standard" method for diagnosing osteoporosis and monitoring changes in BMD over time is dual-energy x-ray absorptiometry (DXA) of the lumbar spine, total proximal femur, femoral neck, and sometimes the 33% (one-third) radius region of interest.[3] Periodontal disease is typically assessed by methods that include visual inspection, probing to measure alveolar crestal height (ACH), and oral radiography to obtain an image of intact teeth and surrounding alveolar bone. There is no standard technology or region of the jaw for measuring oral BMD. Preliminary data suggest that slightly modified dental panoramic radiography could be used as a screening tool to identify patients at high risk for osteoporosis, possibly opening the door for dentists to play a role in improving patient awareness of non-dental skeletal disorders. Despite the recognized limitations of published clinical trials, the United States Surgeon General has stated in *Bone Health and Osteoporosis*, that oral bone loss and tooth loss are associated with osteoporosis, and that osteoporosis and osteopenia may have "an impact on the need for, and the outcomes from, a variety of periodontal and prosthetic procedures."[4] Clearly, however, well-designed long-term prospective clinical trials are needed to validate the relationship between periodontitis and systemic osteoporosis, and to enhance our understanding of the factors linking these two diseases.

Another aspect of the association between osteoporosis and oral bone health concerns the effects of treatment of one

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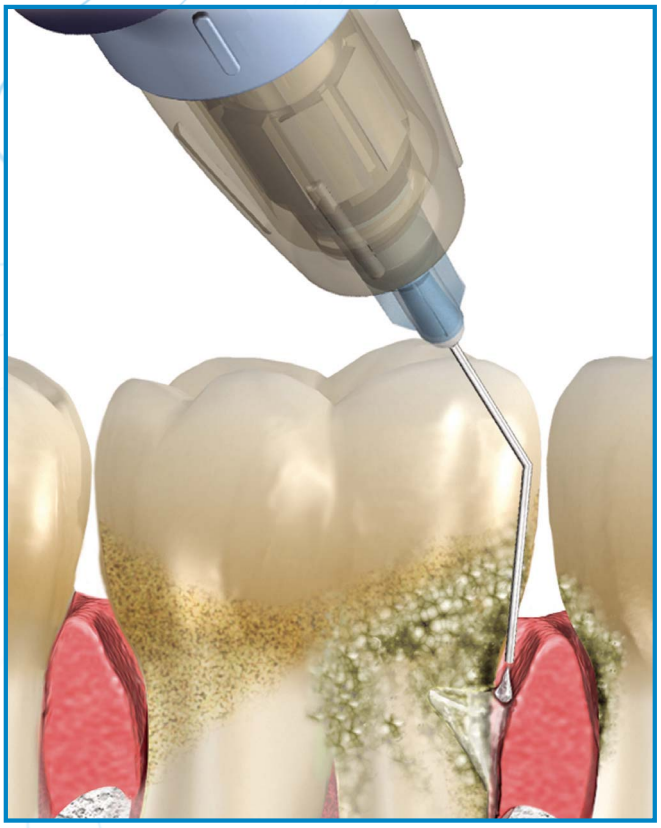

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- **Do not inject.**
- For adults who require localized anesthesia in periodontal pockets during scaling and/or root planing.
- Can be used for a single tooth, quadrant, or the entire mouth.
- Quick 30-second onset
- Oraqix® should not be used in those patients with congenital or idiopathic methemoglobinemia.
- Can be reapplied if needed to a maximum of 5 cartridges.

* vanSteenberge D et al: Patient evaluation of a novel non-injectable anesthetic gel: a multicenter crossover study comparing the gel to infiltration anesthesia during scaling and/or root planing. J Periodontol 2004; 75(11): 1471-1478.

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Brief Summary of Prescribing Information

INDICATIONS AND USAGE
Oraqix® is indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing.

CONTRAINDICATIONS
Oraqix® is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to any other component of the product.

WARNINGS
Prilocaine can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents. Methemoglobinemia has also been reported in a few cases in association with lidocaine treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Oraqix® should not be used in those patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in, e.g., buccal mucous membranes, lips and nail beds. In severe cases symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrhythmia and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if metHb-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia. The diagnosis can be confirmed by an elevated methemoglobin level measured with co-oximetry. Normally, metHb levels are <1%, and cyanosis may not be evident until a level of at least 10% is present. The development of methemoglobinemia is generally dose related. The individual maximum level of metHb in blood ranged from 0.8% to 1.7% following administration of the maximum dose of 8.5 g Oraqix®.

Management of Methemoglobinemia: Clinically significant symptoms of methemoglobinemia should be treated with a standard clinical regimen such as a slow intravenous infection of methylene blue at a dosage of 1-2 mg/kg given over a five minute period.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine are also at greater risk for developing methemoglobinemia. Treatment with Oraqix® should be avoided in patients with any of the above conditions or with a previous history of problems in connection with prilocaine treatment.

PRECAUTIONS
General:
DO NOT INJECT
Oraqix® should not be used with standard dental syringes. Only use these product with the Oraqix® Dispenser, available from DENTSPLY Pharmaceutical.

Allergic and anaphylactic reactions associated with lidocaine or prilocaine can occur. These reactions may be characterized by urticaria, angioedema, bronchospasm, and shock. If these reactions occur they should be managed by conventional means.

Oraqix® coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. A loss of protective reflexes may allow corneal irritation and potential abrasion. If eye contact occurs, immediately rinse the eye with water or saline and protect it until normal sensation returns. In addition, the patient should be evaluated by an ophthalmologist, as indicated.
Oraqix® should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Information for Patients: Patients should be cautioned to avoid injury to the treated area, or exposure to extreme hot or cold temperatures, until complete sensation has returned.

Drug Interactions: Oraqix® should be used with caution in combination with dental injection anesthesia, other local anesthetics, or agents structurally related to local anesthetics, e.g., Class 1 antiarrhythmics such as tocainide and mexiletine, as the toxic effects of these drugs are likely to be additive and potentially synergistic.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
Carcinogenesis - Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or prilocaine. Chronic oral toxicity studies of o-toluidine, a metabolite of prilocaine, have shown that this compound is a carcinogen in both mice and rats. The tumors associated with o-toluidine included hepatocarcinomas/ adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. These findings were observed at the lowest tested dose of 150 mg/kg/day or greater over two years (estimated daily exposures in mice and rats were approximately 6 and 12 times, respectively, the estimated exposure to o-toluidine at the maximum recommended human dose of 8.5g of Oraqix® gel on a mg/m2 basis).

Mutagenesis - o-Toluidine, metabolite of prilocaine, was positive in Escherichia coli DNA repair and phage-induction assays. Urine concentrates from rats treated orally with 300 mg/kg o-toluidine were mutagenic to Salmonella typhimurium in the presence of metabolic activation.

USE IN PREGNANCY:
Teratogenic Effects: Pregnancy Category B
Treatment of rabbits with 15 mg/kg (180 mg/m^2) produced evidence of maternal toxicity and evidence of delayed fetal development, including a non-significant decrease in fetal weight (7%) and an increase in minor skeletal anomalies (skull and sternebral defects, reduced ossification of the phalanges). The effects of lidocaine and prilocaine on post-natal development was examined in rats treated for 8 months with 10 or 30 mg/kg, s.c. lidocaine or prilocaine (60mg/m^2 and 180 mg/m^2 on a body surface area basis, respectively up to 1.4-fold the maximum recommended exposure for a single procedure). This time period encompassed 3 mating periods. Both doses of either drug significantly reduced the average number of pups per litter surviving until weaning of offspring from the first 2 mating periods. Because animal reproduction studies are not always predictive of human response, Oraqix® should be used during pregnancy only if the benefits outweigh the risks.

Nursing Mothers: Lidocaine and, possibly, prilocaine are excreted in breast milk. Caution should be exercised when Oraqix® is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Very young children are more susceptible to methemoglobinemia. There have been reports of clinically significant methemoglobinemia in infants and children following excessive applications of lidocaine 2.5% topical cream (See WARNINGS).

Geriatric Use: In general, dose selection for and elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Following SRP treatment with Oraqix® in 391 patients, the most frequent adverse events were local reactions in the oral cavity (see following table). These events, which occurred in approximately 15% of patients, included pain, soreness, irritation, numbness, vesicles, ulcerations, edema and/or redness in the treated area. Of the 391 patients treated with Oraqix®, five developed ulcerative lesions and two developed vesicles of mild to moderate severity near the site of SRP. In addition, ulcerative lesions in or near the treated area were also reported for three out of 168 patients who received placebo. Other symptoms reported in more than one patient were headache, taste perversion, nausea, fatigue, flu, respiratory infection, musculoskeletal pain and accident/injury.

Table 1. Number (percent) of patients with adverse events occurring in more than one patient in any of the treatment groups. Each patient is counted only once per adverse event. The occurrence in a single patient is included in this table if the same symptom has been seen in at least one patient in another group.

System Organ Class Preferred Team	Oraqix® gel* (N=391) n (%)	Placebo gel (N=168) n (%)	Lidocaine injection* (N=170) n (%)
Muscular-Skeletal System Disorders			
Myalgia	1(0)	2(1)	
Arthralgia and/or Arthropathy	1(0)	1(1)	
Central & Peripheral Nervous System Disorders			
Headache	8(2)	3(2)	5(3)
Dizziness	1(0)	1(1)	1(1)
Special Senses Other, Disorders			
Taste Perversion[1]	8(2)	1(1)	
Gastro-Intestinal System Disorders			
Nausea	3(1)		1(1)
Respiratory System Disorders			
Respiratory Infection	2(1)		1(1)
Rhinitis		2(1)	
Body as a whole-General Disorders			
Accident and/or Injury	2(1)	2(1)	
Fatigue	3(1)		2(1)
Flu-Like Disorder	2(1)		
Pain (remote from application site)	1(0)	1(1)	1(1)
Application Site Disorders**			
Anesthesia Local	2(1)		
Application Site Reaction***	52(13)	20(12)	

[1] includes complaints of bad or bitter taste lasting for up to 4 hours after administration of Oraqix®
* in a cross-over study, 170 subjects received either Oraqix® or lidocaine injection 2% in each test period
** i.e.,symptoms in the oral cavity
*** includes pain, soreness, irritation, numbness, ulcerations, vesicles, edema, abscess and/or redness in the treated area

Allergic Reactions: Allergic and anaphylactic reactions associated with lidocaine or prilocaine can occur. They may be characterized by urticaria, angioedema, bronchospasm, and shock. If they occur, they should be managed by conventional means.

OVERDOSAGE
Local anesthetic toxicity emergency: Oraqix® used at the recommended doses is not likely to cause toxic plasma levels of lidocaine or prilocaine. However, if other local anesthetics are administered at the same time, e.g. topically or by injection, the toxic effects are thought to be additive and could result in an overdose with systemic toxic reactions. There is generally an increase in severity of symptoms with increasing plasma concentrations of lidocaine and/or prilocaine. Systemic CNS toxicity may occur over a range of plasma concentrations of local anesthethics. CNS toxicity may typically be found around 5000 ng/mL of lidocaine, however a small number of patients reportedly may show signs of toxicity at approximately 1000 ng/mL. Pharmacological thresholds for prilocaine are poorly defined. Central nervous system (CNS) symptoms usually precede cardiovascular manifestations. The plasma level of lidocaine observed after the maximum recommended dose (5 cartridges) of Oraqix® in 11 patients exposed over 3 hours ranged from 157-552 ng/mL with a mean of 284 ng/mL ± 122 SD. The corresponding figure for prilocaine was 53-181 ng/mL with a mean of 106 ± 45 SD. (see CLINICAL PHARMACOLOGY, Absorption).

Systemic adverse effects of lidocaine and/or prilocaine are manifested by central nervous system and/or cardiovascular symptoms.

Clinical symptoms of systemic toxicity include CNS excitation and/or depression (light-headedness, hyperacusis, visual disturbances, muscular tremors, and general convulsions). Lidocaine and/or prilocaine may cause decreases in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. Cardiovascular manifestations may include hypotension, bradycardia, arrhythmia, and cardiovascular collapse.

Management of Local Anesthetic Emergencies: Should severe CNS or cardiovascular symptoms occur, these may be treated symptomatically by, for example, the administration of anticonvulsive drugs, respiratory support and/or cardiovascular resuscitation as necessary.

See warnings on methemoglobinemia on Oraqix® full prescribing information at www.oraqix.com.

Management of Methemoglobinemia: Clinically significant symptoms of methemoglobinemia should be treated with a standard clinical regimen such as a slow intravenous injection of methylene blue at a dosage of 1-2 mg/kg given over a five minute period.

DOSAGE AND ADMINISTRATION
The maximum recommended dose of Oraqix® at one treatment session is 5 cartridges, i.e., 8.5g gel.

When administered, Oraqix® should be a liquid. If it has formed a gel, it should be placed in a refrigerator (do not freeze) until it becomes a liquid again. When in the liquid state, the air bubble visible in the cartridge will move if the cartridge is tilted.

DO NOT FREEZE. Some components of Oraqix® may precipitate if cartridges are frozen. Cartridges should not be used if they contain a precipitate.
Do not use dental cartridge warmers with Oraqix®. The heat will cause the product to gel.

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on the other. Particular attention has been focused on the effects, for better or for worse, of treatments for osteoporosis on bone in the jaw. Anti-resorptive (anti-catabolic) therapy for osteoporosis (e.g., estrogen, bisphosphonates) has been associated with improved ACH, increases in mandibular BMD, and tooth retention. There are limited preclinical data suggesting that anabolic therapy for osteoporosis with teriparatide (recombinant human parathyroid hormone 1-84) may also have potential benefits for oral bone health. Long-term follow-up of patients treated with alendronate, the bisphosphonate most commonly used to treat osteoporosis, suggests that it is safe and effective with continuous use for at least 10 years.[5] High doses of injectable bisphosphonates given at frequent dosing intervals for the treatment of cancer or related conditions have been associated with osteonecrosis of the jaw (ONJ).[6] While there have also been some reported cases of ONJ in patients treated for osteoporosis with lower doses of bisphosphonates, whether given orally or by injection, the risk appears to be extraordinarily low at about 0.7 per 100,000 patient-treatment-years.[7] This is far less than the risk of a fragility fracture and less than other risks commonly faced in modern society, such as the risk of death by motor vehicle accident or by homicide.

Until more data are available to better define the relationships between osteoporosis and oral bone health, and until we have a better understanding of the global risks and benefits of therapeutic interventions for one on the other, we must continue to manage our patients with these common disorders. What do we do until the data arrive? Here are a few suggestions:

1. For all healthcare professionals, every patient encounter is an opportunity to improve skeletal and oral bone health by promoting healthy lifestyle measures and discouraging unhealthy behavior. Patients can be counseled on the importance of good nutrition; especially having adequate intake of calcium and vitamin D, the benefits of regular exercise, avoiding tobacco smoking or chewing, and limiting alcohol drinking. Regular medical and dental checkups according to standard guidelines should be recommended.

2. Dental healthcare professionals who care for patients with periodontitis, particularly when there is tooth loosening or tooth loss, can suggest that they may be at risk for osteoporosis, and encourage follow-up by a primary care provider. This may be sufficient to later initiate a risk factor assessment, modification of potentially reversible risk factors, and further diagnostic evaluation by DXA. Some of these patients may benefit from pharmacological intervention to reduce fracture risk.

3. Medical healthcare professionals managing patients with osteoporosis should advise vigilance at maintaining good oral hygiene and having routine dental care. Prior to starting a bisphosphonate for the treatment of osteoporosis, tell the patient there is a very small (but not zero) risk of ONJ. If a tooth extraction or invasive oral surgery is anticipated, it may be prudent to have the procedure completed, and assure bone healing, before starting the bisphosphonate. If the patient is already taking a bisphosphonate for the treatment of osteoporosis and a tooth extraction or invasive oral surgery is planned, consider stopping the bisphosphonate in advance of the procedure and restarting after bone healing has occurred.

Finally, there is a plea for collaboration and communication among dental and medical healthcare professionals. If we, as healthcare providers, have a better understanding of the diverse scientific literature, diagnostic tools, and therapeutic interventions that are used by colleagues in other patient care disciplines, then improved clinical outcomes for our patients are the likely result.

References

1. Mercado F, Marshall RI, Klestov AC, et al. Relationship between rheumatoid arthritis and periodontitis. *J Periodontol*. 2001;72:779-787.
2. Oh T, Bashutski J, Giannobile W. The interrelationship between osteoporosis and oral bone loss. *Grand Rounds Oral-Sys Med.* 2007;2:10-21.
3. Binkley N, Bilezikian JP, Kendler DL, et al. Official positions of the international society for clinical densitometry and executive summary of the 2005 position development conference. *J Clin Densitom*. 2006;9:4-14.
4. US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*. Rockville, MD, US Department of Health and Human Services, Office of the Surgeon General; 2004.
5. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med*. 2004;350:1189-1199.
6. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med.* 2006;144:753-761.
7. American Dental Association Council on Scientific Affairs. Dental management of patients receiving oral bisphosphonate therapy: expert panel recommendations. *J Am Dent Assoc*. 2006;137:1144-1150.

Literature Review

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THE INTERRELATIONSHIP BETWEEN OSTEOPOROSIS AND ORAL BONE LOSS

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Abstract
Osteoporosis is a systemic skeletal disease manifested by reduced bone strength, decreased bone mineral density, and alteration of bony architecture. It can develop when bone resorption significantly overrides bone formation, either through imbalance in the genesis and apoptosis of osteoblasts and osteoclasts or through inappropriate regulation of bone remodeling. Oral bone loss (e.g., periodontitis, tooth loss, and implant bone loss) is caused by breakdown of bone homeostasis in the oral cavity. Both osteoporosis and periodontitis are bone-resorptive, host-dependent, multifactorial diseases, and bone loss is stimulated, systemically or locally, by cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha. Although some contradictory results exist, a large body of literature supports an association between systemic and oral bone loss. Individuals with systemic or oral bone loss should be closely managed with a clinical protocol that minimizes further deterioration of systemic or oral bony structures. Additional studies are needed to clarify the causality and/or association between systemic and oral bone loss and to determine the most efficacious therapeutic approach for the prevention and treatment of systemic/oral bone loss.

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*(A complimentary copy of this article may be downloaded at **www.thesystemiclink.com**.)*

Key Words: Bone loss, osteopenia, osteoporosis, periodontitis, treatment

Introduction

Osteoporosis is a systemic skeletal disease manifested by reduced bone strength, decreased bone mineral density (BMD), and altered macrogeometry and microscopic architecture, and resultant increased risk of fractures. A recent report revealed that osteoporosis affects more than 10 million individuals aged 50 years or more; an additional 33.6 million are affected by osteopenia (low bone mass) and consequently are at risk for osteoporosis and its complications.[1] Because of the positive relationship between age and bone loss, the prevalence of osteoporosis increases from 19% among women 65- to 74- years old to more than 50% in women aged 85 years or more.[1] As the elderly population continues to grow, the number of people aged 50 or more with osteoporosis is expected to increase to 12 million by 2010 and to nearly 14 million by 2020.[1]

In the United States (U.S.) approximately 1.5 million fractures each year are attributable to osteoporosis, as are approximately 500,000 hospitalizations, 800,000 emergency department visits, 2.6 million physician visits, and 180,000 nursing home placements.[1] Worldwide, the morbidity, mortality, and healthcare costs related to osteoporosis and resulting in low-trauma fractures are significant.[1]

Osteoporosis is defined by the World Health Organization (WHO) as a bone mineral density (BMD) that is 2.5 standard deviations (SDs) below the young normal.[2] Osteopenia is defined as a BMD between 1 and 2.5 SDs (Table 1).[2] According to the WHO assessment, the patient is assigned a score that represents a comparison to the average young (25- to 45-year-old) healthy adult of the same gender (a T-score) or to the average healthy age- and sex-matched patient (a Z-score). A

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1-unit change in T-score corresponds to a 1-SD difference in BMD from that in a young, healthy individual of the same gender. Thus, osteoporosis corresponds to a T-score of –2.5 or lower, whereas osteopenia corresponds to a T-score between –1 and –2.5.[2]

A number of methods are currently used to assess bone density, including single-photon absorptiometry, dual-photon absorptiometry (DPA), dual-energy x-ray absorptiometry (DXA), quantitative computed tomography, and radiographic absorptiometry (RA). Of these, DXA is considered the preferred technique for measurement of BMD.[3] DXA measures bone density as "area density" in units of grams per square centimeter. The sites most often used for DXA measurement of BMD include central sites such as the spine or hip, or peripheral sites such as the radius.

Although the etiology of osteoporosis has not been clearly defined, the initiation and progression of osteoporosis are known to be multifactorial. Osteoporosis is frequently seen in postmenopausal women and women who have undergone ovariectomy.[4] The incidence of osteoporosis is dependent on age, gender, menopausal status, environmental factors, and systemic health status, with Caucasian postmenopausal women representing the highest risk group.[4,5] Risk factors for osteoporosis may include, but are not limited to: genetics, aging, early menopause, physical inactivity, heavy smoking, alcohol abuse, low calcium intake, and long-term use of certain medications (e.g., glucocorticoids, antiepileptic agents, gonadotropin-releasing hormone agonists, excessive thyroxine doses, lithium, and anticoagulants). Certain systemic diseases also represent risk factors (e.g., primary hyperparathyroidism, hypogonadism, multiple myeloma, leukemia, rheumatoid arthritis, celiac disease, gastrectomy, and chronic obstructive pulmonary disease), with some of these factors being modifiable (Table 2).[6-8] The guidelines proposed by the North American Menopause Society indicate that some risk groups should be regularly assessed for osteoporosis, including all women aged ≥65 years, all women with a medical condition that can cause bone loss, and younger postmenopausal women who possess a risk factor for osteoporosis.[3]

Table 1: World Health Organization criteria for defining osteoporosis and osteopenia

Condition	Description
Normal	BMD ≤1 SD below the mean for a young, healthy adult (T ≥ –1.0)
Osteopenia	BMD >1 SD, but <2.5 SD below the mean for a young, healthy adult (–1.0 > T > –2.5)
Osteoporosis	BMD ≥2.5 SD below the mean for a young, healthy adult (T ≤ –2.5)
Established osteoporosis	BMD ≥2.5 SD below the mean for a young, healthy adult (T ≤ –2.5), with 1 or more fragility fractures

T score = 1 SD difference from the BMD in a young, healthy adult of the same gender. BMD, bone mineral density; SD, standard deviation; WHO, World Health Organization. Modified from Report of a WHO Study Group[2]

In a healthy individual, bone resorption and bone formation are in equilibrium, allowing the body to maintain bone mass and mineral density. Bone homeostasis is maintained at the cellular level by 2 highly specialized cell types, osteoclasts and osteoblasts, which are responsible for bone resorption and formation, respectively. The bone-remodeling cycle consists of a resorptive phase, which occurs over a 3- to 4-week period, followed by the reversal phase and, finally, the formative phase (Figure 1).[9] During the human life, the formation of a basic multicellular unit (BMU), which includes osteoblasts and osteoclasts, constantly takes place through the coupling of bone formation and resorption.[10] On average, the adult skeleton contains more than 1 million BMUs at any time, with almost 5-fold more located in the trabecular bone compared with the cortical bone.[11]

Bone resorption is initiated via a resorptive stimulus produced by cytokines or mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), parathyroid hormone (PTH), PTH-related protein (PTHrP), prostaglandin E2 (PGE2), and tumor necrosis factor-alpha (TNF-α).[12,13] In response to a specific stimulus, preosteoclasts are recruited from the hematopoietic lineage into the area of bone resorption and differentiate into active osteoclasts.[14] The active multinuclear osteoclasts form resorption pits for active bone resorption. Osteoclasts possess the ruffled membrane and clear zone that ensure the resorption process remains localized beneath the osteoclast, maintaining the pH-regulating proton pump in the bone resorptive microenvironment. Resorption gradually slows and eventually ceases as the active osteoclasts are replaced with transient mononuclear cells; this is the reversal phase. The formative phase then begins with recruitment of pre-osteoblasts (mesenchymal precursor cells) into the site. This is followed by differentiation of pre-osteoblasts into osteoblasts via the action of bone morphogenetic proteins (BMPs). In this stage, some osteoblasts are entrapped in the bone matrix and become osteocytes. Through the coupled process of bone resorption and formation, on average, an exchange of 10% of the

skeleton occurs every year over an individual's lifetime. If there is significant imbalance in the genesis and apoptosis (programmed cell death) of the bone-forming or bone-resorbing cells, osteoporosis or osteopenia may develop. Inappropriate regulation of bone remodeling can also lead to the net bone loss seen in osteopenia and osteoporosis.

Osteoporosis and oral bone loss: association versus causality

Periodontitis, a major cause of tooth loss, is clinically determined by radiographic bone loss and/or clinical attachment loss (CAL). The prevalence of periodontitis in the U.S. population, if defined as at least 1 site with CAL of >2 mm, is approximately 80% in all adults affected by bone loss, and approximately 90% in those aged 55 to 64 years.[15] Although bacterial plaque is the primary cause of periodontitis, host susceptibility or responsiveness is believed to play a major role in the initiation and progression of tissue destruction.[16,17] Both osteoporosis and periodontitis are bone-resorptive, host-dependent, multifactorial diseases, and the bone loss in both diseases is exaggerated, either systemically or locally, by the activity of cytokines (e.g., IL-1 and IL-6). In this section, studies of the relationship between systemic bone loss (i.e., BMD) and oral bone loss (e.g., alveolar bone loss [ABL] and subsequent tooth loss) are explored. A summary of these studies is given in Table 3.

The relationship between systemic BMD and tooth loss was investigated in 1,365 Caucasian early-postmenopausal women.[18] BMD was measured by DXA at the lumbar spine and proximal femur. Among the study population, 445 (33%) were osteoporotic, 694 (51%) were osteopenic, and 226 (16%) had normal BMD. The results revealed no significant correlation between tooth count and systemic BMD, showing that tooth count is not a good indicator of the risk of osteoporosis. The findings in this study correspond to those in a previous cross-sectional study by Elders and colleagues,[19] who demonstrated that there was no significant association between systemic BMD (in this case, lumbar BMD and metacarpal cortical thickness) and clinical parameters of periodontitis, including mean probing depth (PD), bleeding on probing (BOP), alveolar bone height (ABH), and number of missing teeth.

However, other studies[20-22] have shown contradictory results. Klemetti and colleagues[20] conducted a cross-sectional study in 227 healthy postmenopausal women, aged 48 to 56 years, and found a correlation between skeletal BMD and number of remaining teeth in the patient population. Individuals with high skeletal BMD appeared to retain their teeth with deep periodontal pockets more often than did those with osteoporosis. The correlation between systemic BMD and tooth loss was confirmed by a longitudinal study in which 189 Caucasian postmenopausal women were followed for up to 7 years.[22] Systemic BMD was measured at the lumbar spine, femoral neck, and whole body using either DPA or DXA, and the values measured from the 2 different instruments were adjusted. For the 7-year study period, 45 women reported tooth loss, and BMD declined as a whole body (–0.26%/year) and at the femoral neck (–0.02%/year), but increased in the spine (+0.42%/year). The relative risk of tooth loss relative to BMD changes of 1%/year was 4.83 for the body as a whole, 1.50 for the femoral neck, and 1.45 for the spine,

Table 2
Risk factors for osteoporosis

Studies	Risk relationship with osteoporosis	Modifiable with ?
Age	Older	No
Gender	Female	No
Genetics	Predilection	No
Menopause	Early menopause	No
Ethnicity	Asian or Caucasian women	No
Bone mass	Low	Treatment for osteoporosis/osteopenia
Calcium intake	Low	High-calcium diet
Physical activity	Negative	Weight-bearing exercise
Smoking	Positive	Smoking cessation
Alcohol consumption	Positive	Decreased alcohol consumption
Certain systemic diseases (e.g., hyperparathyroidism)	Positive	Treatment of the systemic disease
Certain medications (e.g., glucocorticoids)	Long-term use	Treatment modification if feasible

thus indicating a correlation between systemic BMD and tooth loss. Other independent predictors of tooth loss were years post menopause and number of teeth at baseline.

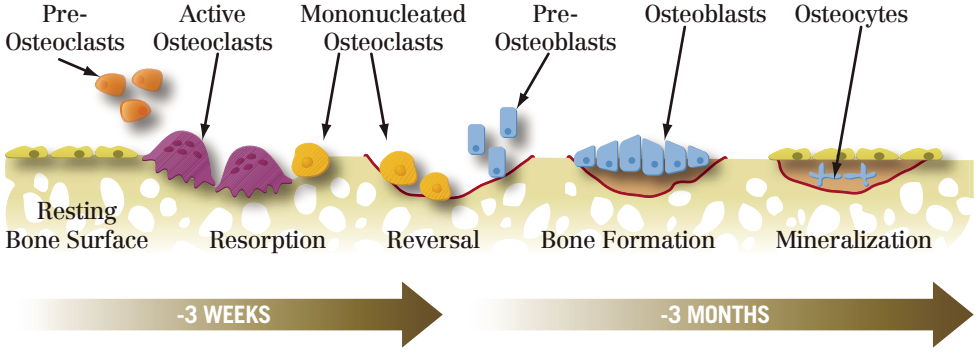
The relationship between systemic and oral bone loss has also been explored using other measures such as hip BMD, metacarpal BMD, lumbar BMD, forearm BMD, presence/absence of osteopenia/osteoporosis, CAL, ABH, and the Community Periodontal Index of Treatment Needs (CPITN).[23-30]

Tezal and colleagues,[26] in a cross-sectional study using 70 dentate postmenopausal Caucasian women aged 51 to 78, evaluated the relationship between systemic bone loss and periodontal disease. Systemic BMD was measured by DXA at the lumbar spine and femur, and periodontal condition of the study population was examined by CAL, ABL, number of remaining teeth, gingival index, plaque index, and calculus index. Multiple linear regression analyses adjusting for age, age at menopause, estrogen supplementation, bone mass index (BMI), smoking, and supragingival plaque, demonstrated that BMDs at all femoral regions and the spine were correlated with ABL (r = –0.20 to –0.27), with statistical significant correlations found for the trochanter, Ward's triangle, and total femur (r = –0.25 to –0.27). Also, CAL was consistently, though not significantly, correlated to spinal and femoral BMD (r = –0.17 and r = –0.10 to –0.16). The results of the study suggested that systemic bone loss may be a risk indicator for periodontal attachment and bone loss.

Inagaki and colleagues[30] studied the relationship between systemic and oral bone loss in 171 premenopausal (mean age: 37.9±8.0 years) and 185 postmenopausal (mean age: 63.3±7.7 years) Japanese women. Metacarpal BMD as measured by computerized radiograph densitometry was used to determine systemic bone loss, whereas CPITN (scored by examiners blinded to the subjects' metacarpal BMD status) was used to determine oral bone loss. The results demonstrated that the proportion of subjects with periodontitis (CPITN = 3 or 4) increased as metacarpal BMD decreased. The odds ratio of osteopenia/osteoporosis to periodontitis was 3.2 (2.0 when adjusted for age and menopausal status). The study also found that postmenopausal women with less than 20 teeth were more likely to have low metacarpal BMD when compared with postmenopausal women with more than 20 teeth (1.6 vs. 1.0). The study suggests that an association may exist between systemic bone loss and periodontitis, independent of age and menopausal status, and that systemic bone mineral status might be related to tooth count in postmenopausal Japanese women.

Causality between systemic and oral bone loss has been tested in several longitudinal studies.[28,29,31] In a 2-year longitudinal study exploring the association between cigarette smoking and ABL in 59 postmenopausal females (38 nonsmokers and 21 smokers), both smokers and osteoporotic/osteopenic subjects experienced mean ABL during the study period.[28] Mean alveolar bone gain was noted only in nonsmokers with normal bone BMD. The results suggest that smoking and osteoporosis/osteopenia can be risk factors for ABL. Recently, Yoshihara and colleagues[29] conducted a 3-year longitudinal study in 179 gender-matched Japanese community-dwelling elderly to investigate the relationship between periodontal disease and systemic BMD. Patients did not smoke or have diabetes, had more than 20 teeth, and were not taking medications for osteoporosis. BMD was measured at the heel using an ultrasound bone densitometer, and the presence/absence of osteopenia was determined by stiffness values (a combination of speed-of-sound and broadband ultrasound attenuation as the signal travels through bone). Stiffness was indicated in the bone densitometer as a percentage of the value for a healthy younger individual. Osteopenia

Figure 1: Bone-remodeling cycle



Source: From "Mediators of periodontal osseous destruction and remodeling: Principles and implications for diagnosis and therapy," published in J Periodontol.

The bone-remodeling cycle begins with the resorptive phase, during which preosteoclasts are recruited and differentiated into active osteoclasts, leading to bone resorption. After active bone resorption, multinucleated osteoclasts are replaced by mononucleated osteoclasts lining the resorption lacunae; this is followed by recruitment of preosteoblasts through coupling (the reversal phase). The recruited preosteoblasts are differentiated into active matrix-secreting cells, forming bone and undergoing mineralization (the formative phase). Recreated from McCauley and Nohutcu.[9]

was defined as a stiffness value ≤85 for 70-year-old males and ≤69 for females. Periodontal disease status was examined by periodontal probing using a pressure-sensitive periodontal probe[i]. At the 3-year follow-up, the number of progressive sites (CAL ≥3mm during the 3 years) was significantly higher in the osteopenic group than in the non-osteopenic group (P< .05). Also, multiple linear regression analysis showed that BMD was associated with the number of progressive sites (CAL ≥3mm during the 3 years) (P=.001), suggesting a significant relationship between periodontal attachment loss and systemic BMD.

Jeffcoat and colleagues[23] examined mandibular basal BMD and hip BMD in 158 postmenopausal women (mean age: 62.2 years) using quantitative digital intraoral radiography and DXA, respectively. The study found a significant correlation between mandibular basal BMD and hip BMD, and suggested that intraoral radiography could serve as a screening tool for osteopenia.

In an older, ethnically diverse population (1,084 subjects aged 60 to 75 years), Persson and colleagues[32] studied the prevalence of self-reported history of osteoporosis, the

Table 3
Studies on the relationship between systemic and oral bone loss

Studies	Population	Oral Measure	Systemic Measure	Study Type	Results
Earnshaw and colleagues[18]	1,365 Caucasian women (45-59 years old	Tooth count	Lumbar/proximal femur/BMD	CS	No relationship
Elders and colleagues[19]	286 women (46-55 years old)	ABH/tooth count	Lumbar BMD/MCT	CS	No relationship
Klemetti and colleagues[20]	227 PM women (48-56 years old)	ABH/tooth count	Skeletal BMD	CS	Correlation
Mohammad and colleagues[21]	30 PM Asian-American women	CAL/tooth count	os calcis BMD	CS	Correlation
Krall and colleagues[22]	189 Caucasian PM women	Tooth loss	Skeletal BMD	7-year LS	Correlation
Jeffcoat and colleagues[23]	158 PM women 62.2±7.6 years	Mandibular basal BMD	Hip BMD	CS	Correlation
Hildebolt and colleagues[24]	135 PM women (41-70 years old)	CAL	Lumbar/proximal femur BMD	CS	Correlation between years of PM and CAL
Kribbs[25]	112 women (50-85 years old)	CAL	OP (yes/no)	CS	No relationship
Tezal and colleagues[26]	70 PM Caucasian women (51-78 years old)	CAL/ABH	Skeletal BMD	CS	Correlation
von Wowern and colleagues[27]	12 OP and 14 normal women	CAL	Forearm BMD	CS	Correlation
Payne and colleagues[28]	38 PM women	ABH/ABD	Normal vs. OP/osteopenia	2-year LS	Correlation
Yoshihara and colleagues[29]	179 Japanese women and men (70 years old)	CAL	Normal vs. osteopenia	3-year LS	Correlation

ABD, alveolar bone density; CS, cross-sectional; LS, longitudinal study; MCT, metacarpal cortical thickness; MRRH, mandibular residual ridge height; OP, osteoporosis; PM, postmenopausal; PRM, premenopausal.

[i]VIVACARE TPS PROBE®, Schaan, Lichtenstein

agreement between panoramic radiographic findings of mandibular cortical index (MCI) and self-reported osteoporosis, and the likelihood of having both a self-reported history of osteoporosis and a diagnosis of periodontitis.[32] The study results demonstrated a positive MCI (indicative of bone loss) in 38.9% of the subjects, whereas only 8.2% of the subjects self-reported osteoporosis. The intraclass correlation between MCI and self-reported diagnosis of osteoporosis was marginal, but statistically significant (0.20, P<.01), and the likelihood of an association between MCI and osteoporosis was 2.6 (P<.01), suggesting an association between osteoporosis and periodontitis. The study also suggests that oral health practitioners can screen osteoporotic elderly individuals by means of dental panoramic radiographs taken for diagnosis of the teeth and jawbones.

In interpreting the above studies, risk indicators must be differentiated from risk factors. A risk indicator is defined as a probable or putative risk factor, detected in case-control or cross-sectional studies, but not confirmed by longitudinal studies. A risk factor is defined as any environmental, behavioral, or biological factor confirmed by a temporal sequence. Risk factors are verified by longitudinal studies and indicate a part of a causal chain. With regard to the relationship between systemic and oral bone loss, primarily cross-sectional studies have been performed, and the findings are somewhat contradictory. These contradictory results may be the result of differing populations, small sample sizes, different methods used to assess BMD, and lack of adequate control of confounding factors (e.g., smoking or concurrent therapies).

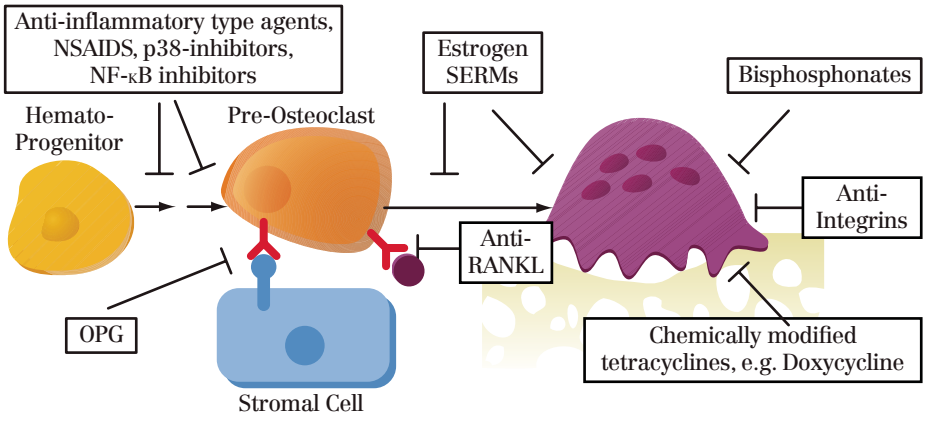
In summary, although the causality between systemic bone loss and oral bone loss has not been determined, the evidence demonstrates a plausible association between the 2 disease entities. Study results imply that individuals with either systemic or oral bone loss should be closely managed with a clinical protocol that minimizes further deterioration of systemic or oral bony structures. Additional randomized, controlled clinical trials are needed to clarify the causality and/or association between systemic and oral bone loss.

Implants and osteoporosis

Osteoporosis results in decreased bone quality and therefore may affect the outcome of dental implant therapy. In an animal study[33] evaluating the effect of glucocorticoid-induced osteoporosis on implant osseointegration, animals received intramuscular injections of glucocorticoids (7.5 mg/kg) for 8 weeks before, simultaneous with, or after implant placement, with a fourth group serving as the control. Although there was no difference in interfacial strength between the test and control groups, bone-to-implant contact (BIC) was significantly lower in the osteoporosis groups (range, 24%±16% to 42%±16%) compared with the control group (49%±10%). Similarly, another study[34] utilizing an ovariectomized rat model found that an osteoporotic state resulted in decreased BIC compared with controls. Furthermore, the greatest decrease in BIC was noted when an osteoporotic state was induced after osseointegration had occurred (BIC = 50% compared with 79% in the control group). The results of these studies imply that although osseointegration of implants in osteoporotic bone is possible, the long-term stability of the implants may be compromised by the disease.

Several studies[35-37] in humans have reported successful implant placement in osteoporotic individuals, although 1 case report[38] revealed that 5 implants failed in a patient 6 months after diphosphonate therapy was initiated. Becker and colleagues[39] conducted a case-control study in 98 patients, half of whom had osteoporosis, and found no correlation between DXA scores and implant failure. This study suggested that an assessment of bone quality at the implant site may be more valuable in predicting implant

Figure 2: Chemotherapeutics for treating systemic/oral bone loss



Source: From "Novel host response therapeutic approaches to treat periodontal diseases," published in Periodontol 2000.

Current approaches to treatment encompass 2 main categories of drugs: anti-resorptive agents and anabolic agents. NSAIDs, anti-RANKL agents, and OPG agents inhibit osteoclast differentiation and formation, whereas estrogen and SERMs inhibit osteoclast activity and promote osteoclast apoptosis. In addition, bisphosphonates promote osteoclast apoptosis, and anti-integrins block matrix adhesion, preventing osteoclastic bone resorption. Tetracyclines and their derivatives reduce MMP activity and consequent degradation of the organic matrix. Recreated from Kirkwood and colleagues.[42]

failure than DXA scores. A retrospective study[40] analyzing 16 osteoporotic patients who received implant therapy showed an overall implant survival rate of 97% in the maxilla and 97.3% in the mandible with a follow-up time of 6 months to 11 years. In addition, the marginal bone loss observed was consistent with that in other studies conducted in nonosteoporotic patients, indicating that osteoporosis does not adversely affect implant success. In contrast, von Wowern and Gotfredsen[41] evaluated whether the presence of mandibular osteoporosis increased marginal bone loss around implants over a 5-year period. No implant failures occurred in any of the 7 osteoporotic and 11 healthy patients, although marginal bone loss increased around the implants placed in patients with osteoporosis.

This literature review demonstrates that dental implants are a viable treatment option for patients with osteoporosis, although less BIC is attainable and there is a higher risk for marginal bone loss. More studies are needed to determine the long-term effects of osteoporosis in this patient population.

Chemotherapeutic agents for treatment of systemic/oral bone loss

Current approaches to treating systemic/oral bone loss with chemotherapeutic agents encompass 2 types of agents: anti-resorptive agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], matrix metalloproteinase [MMP] inhibitors, and bisphosphonates) and anabolic agents (e.g., estrogen and selective estrogen receptor modulators [SERMs] and teriparatide [PTH]). Anti-resorptive agents alter the host response by targeting various cell types in order to minimize net bone resorption. Frequently this involves inhibiting osteoclast activity through numerous mechanisms. Conversely, anabolic agents act to increase net bone deposition, through both stimulation of osteoblast activity and inhibition of osteoclastic bone resorption. Both therapeutic strategies target various steps in the osteoclast differentiation and resorption pathways (Figure 2).[42] These include inhibiting early differentiation signals, such as those from cytokines and inflammatory mediators (e.g., PGE_2 and cyclo-oxygenase 2 [COX-2] inhibitors). Other approaches include preventing osteoclast differentiation by manipulating the receptor activator of the NF-κB ligand (RANKL) pathway through decoy receptors such as osteoprotegerin (OPG), anti-RANKL therapeutic agents, or estrogen/SERMs. Finally, many chemotherapeutic agents are designed to prevent osteoclastic bone resorption by altering osteoclast function. This may include preventing osteoclast adhesion to the bone substrate, preventing formation of the resorptive sealing zone, or inducing premature osteoclast apoptosis. Other types of therapeutic agents, such as PTH, have unknown mechanisms of action. This section will briefly discuss the chemotherapeutic agents used for systemic/oral bone loss along with relevant studies of those agents (Tables 4a and 4b).

Anti-resorptive agents

NSAIDs. Inflammation-induced bone resorption is mediated in part by arachidonic acid metabolites, including prostaglandins and COX-2. These substances are increased in areas of inflammation, notably in the gingiva of periodontitis patients, and they stimulate bone resorption by enhancing expression and potentiating the effects of RANKL.[43-45] NSAIDs inhibit the production of these inflammatory mediators and consequently are used to inhibit osteoclast formation and thereby decrease oral bone loss.[46,47] Williams and colleagues[48] studied the effects of flurbiprofen on naturally occurring periodontitis in a canine model. In this study, beagle dogs were treated with either surgical or nonsurgical periodontal therapy in combination with either flurbiprofen or placebo. For up to 12 months, flurbiprofen significantly decreased the rate of radiographic ABL; this same result did not occur in the placebo group. A human case-control study of 22 patients taking NSAIDs for other medical conditions (e.g., arthritis) found that these patients, when compared with matched controls, displayed lower Gingival Index (GI) scores and shallower pocket depths.[49] A 3-year longitudinal trial[50] assessed the effects of NSAIDs on periodontal disease progression in 44 adult patients with advanced periodontitis. Following periodontal therapy, patients self-administered 50 mg flurbiprofen or placebo twice daily (bid) for 24 months. After 3 years, 33 compliant patients were available for follow-up. Flurbiprofen significantly arrested the progression of bone loss in these patients when compared with controls. Use of these drugs for prevention of oral bone loss has decreased in recent years because of the need for long-term systemic administration and the resultant side effects,[51] although local-delivery applications are being pursued with some success.[52]

MMP inhibitors. MMPs are enzymes that play an important role in extracellular matrix remodeling. MMP activity is increased in areas of inflammation, including periodontitis, leading to unwanted amounts of tissue destruction.[53] Studies have shown that reducing MMP levels in areas of periodontal destruction results in positive clinical outcomes.

Therapeutically, several medications are available to decrease MMP levels. These include bisphosphonates (discussed in the next section), tetracyclines and tetracycline derivatives, and synthetic anticollagenases (e.g., low-dose doxycycline [LDD]). Tetracyclines and their derivatives have the ability to chelate the cations of MMPs, inhibiting their function.[54] Tetracyclines can also inhibit neutrophil and osteoclast activity, thereby limiting their destructive capabilities.[54] MMP inhibition by tetracyclines occurs independently of the antibiotic properties of these agents.

Consequently, chemically modified tetracyclines have been developed that inhibit MMP activity without antimicrobial properties and their resultant side effects.[55] Alternatively, low-dose tetracyclines can also be used to achieve the same therapeutic goal.[56] One randomized 12-month study[57] of patients with chronic periodontitis examined the effects of nonsurgical periodontal therapy administered with and without LDD on MMP-8 levels in gingival crevicular fluid (GCF) and other clinical parameters. Patients who received LDD demonstrated significantly reduced MMP-8 levels for up to 6 months and also significantly reduced probing depths (PD) and GI scores for up to 12 months when compared with patients who did not receive LDD. Low-dose and chemically modified tetracyclines show promise as a therapeutic treatment for oral bone loss.

LDD therapy has also been shown to reduce oral fluid levels of MMP-8 and MMP-13 as well as levels of bone collagen breakdown fragments (cross-linked carboxyterminal telopeptide of type I collagen [ICTP]) when compared with placebo in patients with severe periodontitis and oral bone loss.[57-60] MMP-8 is the predominant type of collagenase found in diseased periodontal tissues and initiates the degradation of collagen.[61,62] Although MMP-8 reduction was also observed after mechanical periodontal therapy, LDD further suppressed MMP-8 levels, confirming the host-modulation effect of LDD. MMP-13 and ICTP are related to bone resorption, and their decrease after LDD therapy is consistent with the ability of LDD to function as a bone-sparing agent for potential applications in the management of osteoporosis.[59,63]

Table 4a
Chemotherapeutic agents for systemic/oral bone loss — anti-resorptive agents

Therapy	Mechanisms of action	Studies	Outcome
Anti-inflammatory agents	Inhibit inflammatory mediator production (PGE_2 and COX-2)	Williams and colleagues[48]	Flurbiprofen decreased radiographic bone loss at 12 mo.
		Waite and colleagues[49]	Lower GI and PDs in patients taking NSAIDs
		Williams and colleagues[50]	Flurbiprofen arrested bone loss progression over 3 yrs.
Bisphosphonates	Inhibit formation and resorptive capacity of osteoclasts Increase osteoclast apoptosis Inhibit MMP production Inhibit inflammatory mediator production	Reddy and colleagues[68]	Alendronate increased bone mass in dogs, but had no effect on periodontal parameters
		Tani-Ishii and colleagues[69]	Incadronate increased BMD and decreased PMN infiltration in rats
		Lane and colleagues[71]	Bisphosphonates improved CAL, PD, and BOP but did not increase BMD
		El-Shinnawi and El-Tantawy[72]	Alendronate increased BMD, but no effect on periodontal parameters
		Takaishi and colleagues[73]	Etidronate increased BMD density and decreased tooth mobility and PDs
MMP inhibitors	Inhibit MMP production Inhibit neutrophil and osteoclast activity	Emingil and colleagues[57]	LDD significantly reduced MMP-8 levels up to 6 mo. and significantly reduced PDs and GI indices up to 12 mo.
OPG	Inhibits osteoclast development	Bolon and colleagues[94]	Adenoviral delivery of OPG reduced bone loss in ovariectomized mice
		Bekker and colleagues[97]	A single injection of OPG reduced bone turnover in postmenopausal women for up to 6 wks.

Bisphosphonates. Bisphosphonates inhibit bone resorption through multiple mechanisms, although the main mechanisms involve inhibiting the formation and resorptive capabilities of osteoclasts and promoting osteoclast apoptosis.[13] Bisphosphonates also downregulate levels of several MMPs, including MMP-1, -3, -7 through -9, and -12 through -14,[64] even in the periodontal ligament cells.[65] Furthermore, some bisphosphonates have anti-inflammatory properties and inhibit the release of inflammatory mediators such as IL-6, TNF-α , and IL-1Beta.[66] Other research[67] suggests that secretion of osteocalcin by osteoblasts may also be affected by these drugs.

Preclinical studies[68,69] evaluating the effect of bisphosphonates on the periodontium reveal that although bisphosphonates prevent oral bone loss compared with controls, they provide no additional benefits in terms of reducing inflammation or PDs. Reddy and colleagues[68] studied the effects of alendronate on oral bone loss in 16 beagle dogs with naturally occurring periodontitis. At 6 months, alendronate resulted in a statistically significant difference in bone mass, although no differences in gingival inflammation, plaque, tooth mobility, or CAL were found when compared with controls. Similarly, another study[69] evaluated the ability of incadronate to prevent oral bone resorption in *Porphyromonas gingivalis*–induced periodontitis and found that it increased BMD and decreased polymorphonuclear leukocyte infiltration compared with controls. Human trials[70-73] have also provided conflicting results. A recent study[72] evaluating the effect of alendronate on ABL in 24 periodontitis patients over 6 months found that the use of this agent increased BMD, but provided no additional benefit for clinical parameters such as PD, CAL, and GI. However, a 12-month randomized controlled trial[71] found different results: Bisphosphonate therapy improved clinical parameters (CAL, PD, and BOP) when compared with placebo, but did not affect periodontal bone mass. In contrast, a long-term study[73] of 4 women receiving intermittent cyclical doses of etidronate revealed that bisphosphonates increased BMD and decreased tooth mobility and PDs. Bisphosphonates are highly concentrated in bone tissue and remain in the body for as long as 10 years.[74] Given this long half-life and recent reports of significant side effects such as osteonecrosis of the jaw,[75] additional research is urgently needed to determine appropriate uses for these drugs. Discussion and a case report on bisphosphonate-related osteonecrosis of the jaw are presented elsewhere in this issue.[76]

Receptor Activator of NF-κ (RANK), RANKL, and OPG. Osteotrophic factors such as hormones (e.g., vitamin D3, PTH, PTHrP), cytokines (IL-1, -6, -11, and -17), growth factors (TNF-α, and BMP-2) and other molecules (PGE_2, CD40L, and glucocorticoids) all enhance the expression of

Table 4b
Chemotherapeutic agents for systemic/oral bone loss — anabolic agents

Therapy	Mechanisms of action	Studies	Outcome
HRT/SERMs	Prevent cytokine production	Lopez-Marcos and colleagues[99]	HRT resulted in decreased PDs, less tooth mobility, and less dental pain
		Norderyd and colleagues[101]	Estrogen supplements decreased gingival bleeding
PTH	Specific mechanism unknown; anabolic actions in bone at intermittent low doses	Miller and colleagues[104]	PTH significantly increased crestal bone levels in ovariectomized rats
		Barros and colleagues[105]	PTH decreased bone resorption and inflammatory cell infiltrate in dogs
		Padbury and colleagues[106]	Hyperparathyroidism patients had increased tori and exostoses, but not increased periodontal disease
		Schneider and colleagues[107]	Intramembranous bone more amenable than endogenous vertebral bone to regeneration with PTH treatment

BOP, bleeding on probing; PMN, polymorphonuclear leukocyte; PTH, parathyroid hormone

the RANKL gene in bone-forming cells.[77,78] The RANKL–RANK interaction is responsible for the differentiation and maturation of osteoclast precursor cells to activate osteoclasts. OPG acts as a decoy receptor expressed by osteoblastic cells that binds to RANKL and inhibits osteoclast development.

Several studies have shown the opposite effect of RANKL and OPG in bone modulation. In pathologic bone resorption observed in bone metabolic conditions, inflammatory diseases, and certain types of cancer, the equilibrium of this interaction is dysregulated. In periodontal disease, the role of RANKL in alveolar bone resorption was first investigated by Teng and colleagues.[79] Several previous studies had suggested that T cells could modulate inflammation and/or alveolar bone resorption, but the mechanism by which host immune responses contribute to alveolar bone destruction remained unclear. Teng and colleagues orally inoculated severe combined immunodeficiency (SCID) mice with the periodontal pathogen, *Actinobacillus actinomycetencomitans*, which resulted in the upregulation of RANKL and alveolar bone destruction. This result suggests that RANKL expression by T cells plays a significant role in the bone destruction observed in periodontitis. Liu and colleagues[80] and Crotti and colleagues[81] demonstrated an overexpression of RANKL in inflamed periodontal tissues, suggesting expression by inflammatory cells. Also, the RANKL:OPG ratio was increased in subjects with periodontitis when compared with healthy subjects, suggesting that this molecular interaction may play an important role in modulating local bone loss. The RANKL:OPG ratio was found to be significantly increased in the GCF of patients with periodontitis when compared with healthy patients.[82] Delivery of OPG has been shown to be beneficial in blocking bone resorption in experimentally induced periodontitis.[83]

Preclinical studies[84-87] demonstrated a potential therapeutic role for OPG in the prevention and reduction of lytic bone lesions associated with skeletal tumors, prostatic carcinoma metastases, hypercalcemia of malignancy, and breast cancer. OPG blocked the increased osteoclast formation responsible for resorptive processes in patients with rheumatoid arthritis[88-90] and in periprosthetic bone tissue.[91-93] Gene therapy to provide life-long OPG delivery has also been proposed as a more practical treatment for chronic inflammatory diseases. OPG-expressing adenoviral (Ad) vectors provided sustained and efficacious levels of circulating OPG that enhanced BMD and reduced the number of osteoclasts for an extended period of time (18 months) in ovariectomized animals.[94] A gene therapy vector co-expressing OPG and administered in a single injection demonstrated complete inhibition of bone breakdown in a periprosthetic bone resorption model[95] and reversed osteopenia in ovariectomized animals, without resulting in liver toxicity.[96] OPG administered by single injection to postmenopausal women resulted in a significant decrease in bone collagen degradation products measured in urine, without adverse side effects, suggesting a potential use for OPG in osteoporosis treatment.[97] The anti-resorptive effect of a genetically engineered OPG-Fc construct was shown to be effective in inhibiting bone resorption in lytic bone disease associated with multiple myeloma.[98] In summary, based on preclinical animal studies and preliminary human studies, the OPG-RANKL-RANK axis is a new target for the treatment of destructive periodontal disease and other bone resorption–related diseases. Additional studies are needed to determine the most efficacious therapeutic approach to that molecular interaction.

Anabolic agents

Estrogen and SERMs. Estrogen functions to maintain bone mass, and its withdrawal leads to accelerated bone resorption, increased osteoclast activity, and subsequent bone loss. This loss of bone mass associated with estrogen deficiency may also occur in the oral cavity. Many studies have linked features characteristic of oral bone loss (tooth loss, decreased oral bone density, and crestal ABL) to both osteoporotic and estrogen-deficient states (see Table 3). Hormone replacement therapy (HRT) using estrogen is well established as a first-line treatment for osteoporosis and is being studied as a way to prevent oral bone loss. SERMs, a class of drugs modified from estrogen, have been developed to provide the specific therapeutic effects of estrogen therapy without unwanted side effects. In terms of treating oral bone loss, the therapeutic goals include blocking cytokine production to decrease osteoclast resorption, which results in increased bone mass. In 1 study[99] evaluating the effects of HRT on the periodontium, patients who received HRT had decreased probing depths, less tooth mobility, and less dental pain compared with controls. Another study[100] found similar results: osteoporotic/osteopenic patients who received estrogen supplementation had a reduced frequency of CAL compared with those who did not receive supplementation.

However, the benefits of HRT remain controversial. In 1 study,[101] 228 women were evaluated for estrogen intake and periodontal status. After controlling for confounding variables, the only significant effect of estrogen on the periodontium was decreased gingival bleeding. Although more controlled studies are needed, SERMs appear to have excellent therapeutic potential for minimizing oral bone loss.

PTH. PTH is an endogenous hormone with potent anabolic and catabolic actions in bone. Clinically, it increases BMD and prevents osteoporotic fractures, and consequently, it is used in the treatment of osteoporosis.[102,103] Although the effects of PTH on the oral cavity are largely unknown, ani-

mal studies suggest that oral bone structure is responsive to the anabolic actions of PTH.[104] Miller and colleagues[104] examined the ability of intermittent PTH therapy to stimulate bone formation in the mandible and humerus of ovariectomized rats. PTH significantly increased crestal bone levels in the mandible, particularly on the buccal surface, when measured at 1 year post ovariectomy. Furthermore, a recent animal study[105] showed that PTH was able to reverse periodontal bone loss in a rodent model. In the study, experimental periodontitis was induced in rats. Animals in the test group were administered PTH in a dose of 40 µg/kg. Histologic examination revealed a significant decrease in bone resorption and decreased inflammatory cell infiltrate in these animals compared with control animals. A study[106] of patients with hyperparathyroidism revealed that these patients did not have an increase in periodontal disease as measured by attachment levels, but they had a higher prevalence of tori and exostoses, indicating an increased level of osseous activity. These findings suggest that the oral cavity is not adversely affected by increased circulating levels of PTH. In fact, the oral cavity may respond more favorably than other areas of the body to PTH therapy. One study[107] found that intramembranous bone was more amenable to regeneration than endogenous vertebral bone when both were treated with PTH. Although PTH is not used specifically to treat oral bone loss, systemic administration may have positive benefits on the oral cavity. Current knowledge of PTH suggests that such treatment may have a positive impact on osseous healing in the oral cavity.

Summary and future research

Both osteoporosis and periodontitis are common bone-resorptive, host-dependent, multifactorial diseases that generally affect older patients. Both diseases are stimulated by bone-resorptive proinflammmatory cytokines such as IL-1 and TNF-α, but the end result of this stimulation differs in the 2 diseases. Osteoporosis results in bone loss that is generalized throughout the skeleton, whereas periodontitis results on bone loss that is localized to the alveolus. Current studies suggest a plausible association between these 2 diseases; however, the causality between them must be clarified with additional randomized controlled clinical trials. There are 2 types of chemotherapeutic agents for the treatment of systemic/oral bone loss: anti-resorptive agents (which inhibit bone loss) and anabolic agents (which increase bone formation). Anti-resorptive agents include NSAIDs, MMP inhibitors, bisphosphonates, RANKL, RANK, and OPG agents. Anabolic agents include SERMs and PTH. Preclinical animal studies and preliminary human trials suggest that these chemotherapeutic agents possess a high potential for use in the treatment of destructive periodontal disease and other bone resorption–related diseases, but additional studies are needed to determine the most efficacious therapeutic approach.

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References

1. US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General.* Rockville, MD: US Dept of Health and Human Services, Public Health Service, Office of the Surgeon General, 2004.
2. Report of a WHO study group. Assessment of osteoporotic fracture risk and its application to screening for postmenopausal osteoporosis. *World Health Organ Tech Rep Ser.* 1994;843:1-129.
3. North American Menopause Society. Management of postmenopausal osteoporosis: position statement of the North American Menopause Society. *Menopause*. 2002;9:84-101.
4. Ballard PA, Purdie DW, Langton CM, et al. Prevalence of osteoporosis and related risk factors in UK women in the seventh decade: osteoporosis case finding by clinical referral criteria or predictive model? *Osteoporos Int.* 1998;8:535-539.
5. Dennison E, Yoshimura N, Hashimoto T, et al. Bone loss in Great Britain and Japan: a comparative longitudinal study. *Bone.* 1998;23:379-382.
6. Lewiecki EM, Kendler DL, Kiebzak GM, et al. Special report on the official positions of the International Society for Clinical Densitometry. *Osteoporos Int.* 2004;15:779-784.
7. Eastell R. Treatment of postmenopausal osteoporosis. *N Engl J Med.* 1998;338:736-746.
8. Lewiecki EM. Management of osteoporosis. *Clin Mol Allergy.* 2004;2:9.
9. McCauley LK, Nohutcu RM. Mediators of periodontal osseous destruction and remodeling: principles and implications for diagnosis and therapy. *J Periodontol.* 2002;73:1377-1391.
10. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev. 2000*;21:115-137.
11. Parfitt AM. Osteonal and hemi-osteonal remodeling: The spatial and temporal framework for signal traffic in adult human bone. *J Cell Biochem.* 1994;55:273-286.
12. Gay CV, Weber JA. Regulation of differentiated osteoclasts. *Crit Rev Eukaryot Gene Expr.* 2000;10:213-230.
13. Rodan GA, Martin TJ. Therapeutic approaches to bone diseases. *Science.* 2000;289:1508-1514.

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14. Giannobile WV. Periodontal tissue engineering by growth factors. *Bone.* 1996;19:23S-37S.
15. US Department of Health and Human Services, National Center for Health Statistics. Public Use Data File No. 7-0627. Third National Health and Nutrition Examination Survey, 1988-1994;1997
16. Loeshce WJ. Clinical and microbiological aspects of chemotherapeutic agents used according to the specific plaque hypothesis. *J Dent Res.* 1979;58:2404-2412.
17. Teng YT. The role of acquired immunity and periodontal disease progression. *Crit Rev Oral Biol Med.* 2003;14:237-252.
18. Earnshaw SA, Keating N, Hosking DJ, et al. Tooth counts do not predict bone mineral density in early postmenopausal Caucasian women. EPIC study group. *Int J Epidemiol.* 1998;27:479-483.
19. Elders PJ, Habets LL, Netelenbos JC, et al. The relation between periodontitis and systemic bone mass in women between 46 and 55 years of age. *J Clin Periodontol.* 1992;19:492-496.
20. Klemetti E, Collin HL, Forss H, et al. Mineral status of skeleton and advanced periodontal disease. *J Clin Periodontol.* 1994;21:184-188.
21. Mohammad AR, Hooper DA, Vermilyea SG, et al. An investigation of the relationship between systemic bone density and clinical periodontal status in post-menopausal Asian-American women. *Int Dent J.* 2003;53:121-125.
22. Krall EA, Garcia RI, Dawson-Hughes B. Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. *Calcif Tissue Int.* 1996;59:433-437.
23. Jeffcoat MK, Lewis CE, Reddy MS, et al. Post-menopausal bone loss and its relationship to oral bone loss. [erratum appears in Periodontol 2000. 2001;26:169]. *Periodontol 2000.* 2000;23:94-102.
24. Hildebolt CF, Pilgram TK, Dotson M, et al. Attachment loss with postmenopausal age and smoking. *J Periodontal Res.* 1997;32:619-625.
25. Kribbs PJ. Comparison of mandibular bone in normal and osteoporotic women. *J Prosthet Dent.* 1990;63:218-222.
26. Tezal M, Wactawski-Wende J, Grossi SG, et al. The relationship between bone mineral density and periodontitis in postmenopausal women. *J Periodontol.* 2000;71:1492-1498.
27. von Wowern N, Klausen B, Kollerup G. Osteoporosis; a risk factor in periodontal disease. *J Periodontol.* 1994;65:1134-1138.
28. Payne JB, Reinhardt RA, Nummikoski PV, et al. The association of cigarette smoking with alveolar bone loss in postmenopausal females. *J Clin Periodontol.* 2000;27:658-664.
29. Yoshihara A, Seida Y, Hanada N, et al. A longitudinal study of the relationship between periodontal disease and bone mineral density in community-dwelling older adults. *J Clin Periodontol.* 2004;31:680-684.
30. Inagaki K, Kurosu Y, Yoshinari N, et al. Efficacy of periodontal disease and tooth loss to screen for low bone mineral density in Japanese women. *Calcif Tissue Int.* 2005;77:9-14.
31. Payne JB, Reinhardt RA, Nummikoski PV, et al. Longitudinal alveolar bone loss in postmenopausal osteoporotic/osteopenic women. *Osteoporos Int.* 1999;10:34-40.
32. Persson RE, Hollender LG, Powell LV, et al. Assessment of periodontal conditions and systemic disease in older subjects. I. Focus on osteoporosis. *J Clin Periodontol.* 2002;29:796-802.
33. Keller JC, Stewart M, Roehm M, et al. Osteoporosis-like bone conditions affect osseointegration of implants. *Int J Oral Maxillofac Implants.* 2004;19:687-694.
34. Cho P, Schneider GB, Krizan K, et al. Examination of the bone-implant interface in experimentally induced osteoporotic bone. *Implant Dent.* 2004;13:79-87.
35. Fjuimoto T, Niimi A, Nakai H, et al. Osseointegrated implants in a patient with osteoporosis: a case report. *Int J Oral Maxillofac Implants.* 1996;11:539-542.
36. Eder A, Watzek G. Treatment of a patient with severe osteoporosis and chronic polyarthritis with fixed implant-supported prosthesis: a case report. *Int J Oral Maxillofac Implants.* 1999;14:587-590.
37. Degidi M, Piattelli A. Immediately loaded bar-connected implants with an anodized surface inserted in the anterior mandible in a patient treated with diphosphonates for osteoporosis: a case report with a 12-month follow-up. *Clin Implant Dent Relat Res.* 2003;5:269-272.
38. Starck WJ, Epker BN. Failure of osseointegrated dental implants after diphosphonate therapy for osteoporosis; a case report. *Int J Oral Maxillofac Implants.* 1995;10:74-78.
39. Becker W, Hujoell PP, Becker BE, et al. Osteoporosis and implant failure: an exploratory case-control study. *J Periodontol.* 2000;71:625-631.
40. Friberg B, Ekestubbe A, Mellstrom D, et al. Branemark implants and osteoporosis; a clinical exploratory study. *Clin Implant Dent Relat Res.* 2001;3:50-56.
41. von Wowern N, Gotfredsen K. Implant-supported overdentures, a prevention of bone loss in edentulous mandibles? A 5-year follow-up study. *Clin Oral Implants Res.* 2001;12:19-25.
42. Kirkwood KL, Cirelli JA, Rogers JE, et al. Novel host response therapeutic approaches to treat periodontal diseases. *Periodontol 2000.* 2007;43:294-315.
43. Ono K, Kaneko H, Choudhary S, et al. Biphasic effect of prostaglandin E2 on osteoclast formation in spleen cell cultures: role of the EP2 receptor. *J Bone Miner Res.* 2005;20:23-29.
44. Li X, Pilbeam CC, Pan L, et al. Effects of prostaglandin E2 on gene expression in primary osteoblastic cells from prostaglandin receptor knockout mice. *Bone.* 2002;30:567-573.
45. Zhang F, Engebretson SP, Morton RS, et al. The overexpression of cyclo-oxygenase-2 in chronic periodontitis. *J Am Dent Assoc.* 2003;134:861-867.
46. Salvi GE, Williams RC, Offenbacher S. Nonsteroidal anti-inflammatory drugs as adjuncts in the management of periodontal diseases and peri-implantitis. *Curr Opin Periodontol.* 1997;4:51-58.
47. Paquette DW, Williams RC. Modulation of host inflammatory

mediators as a treatment strategy for periodontal diseases. *Periodontol 2000.* 2000;24:239-252.
48. Williams RC, Jeffcoat MK, Kaplan ML, et al. Flurbiprofen: a potent inhibitor of alveolar bone resorptions in beagles. *Science.* 1985;227:640-642.
49. Waite IM, Saxton CA, Young A, et al. The periodontal status of subjects receiving non-steroidal anti-inflammatory drugs. *J Periodontal Res.* 1981;16:100-108.
50. Williams RC, Jeffcoat MK, Howell TH, et al. Altering the progression of human alveolar bone loss with the non-steroidal anti-inflammatory drug flurbiprofen. *J Periodontol.* 1989;60:485-490.
51. Verburg KM, Maziasz TJ, Weiner E, et al. Cox-2-specific inhibitors: definition of a new therapeutic concept. *Am J Ther.* 2001;8:49-64.
52. Paquette DW, Lawrence HP, McCombs GB, et al. Pharmacodynamic effects of ketoprofen on crevicular fluid prostanoids in adult periodontitis. *J Clin Periodontol.* 2000;27:558-566.
53. Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. *J Cell Sci.* 2002;115:3719-3727.
54. Rifkin BR, Vernillo AT, Golub LM. Blocking periodontal disease progression by inhibiting tissue-destructive enzymes: a potential therapeutic role for tetracyclines and their chemically-modified analogs. *J Periodontol.* 1993;64:819-827.
55. Golub LM, McNamara TF, D'Angelo G, et al. A non-antibacterial chemically-modified tetracycline inhibits mammalian collagenase activity. *J Dent Res.* 1987;66:1310-1314.
56. Sorsa T, Ding Y, Salo T, et al. Effects of ettracyclines on neutrophil, gingival, and salivary collagenases. A functional and western-blot assessment with special reference to their cellular sources in periodontal diseases. *Ann N Y Acad Sci.* 1994;732:112-131.
57. Emingil G, Atilla G, Sorsa T, et al. The effect of adjunctive low-dose doxycycline therapy on clinical parameters and gingival crevicular fluid matrix metalloproteinase-8 levels in chronic periodontitis. *J Periodontol.* 2004;75:106-115.
58. Gurkan A, Cinarcik S, Huseyinov A. Adjunctive subantimicrobial dose doxycycline: effect on clinical parameters and gingival crevicular fluid transforming growth factor-beta levels in severe, generalized chronic periodontitis. *J Clin Periodontol.* 2005;32:244-253.
59. Gapski R, Barr JL, Sarment DP, et al. Effect of systemic matrix metalloproteinase inhibition on periodontal wound repair: a proof of concept trial. *J Periodontol.* 2004;75:441-452.
60. Lee JY, Lee YM, Shin SY, et al. Effect of subantimicrobial dose doxycycline as an effective adjunct to scaling and root planing. *J Periodontol.* 2004;75:1500-1508.
61. Sorsa T, Uitto VJ, Suomalainen K, et al. Comparison of interstital collagenases from human gingiva, sulcular fluid and polymorphonuclear leukocytes. *J Periodontal Res.* 1988;23:386-393.
62. Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med.* 1989;320:365-376.
63. Golub LM, Lee HM, Greenwald RA, et al. A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis. *Inflamm Res.* 1997;46:310-319.
64. Teronen O, Heikkila P, Konttinen YT, et al. MMP inhibition and downregulation by bisphosphonates. *Ann N Y Acad Sci.* 1999;878:453-465.
65. Nakaya H, Osawa G, Iwasaki N, et al. Effects of bisphosphonates on matrix metalloproteinase enzymes in human periodontal ligament cells. *J Periodontal.* 2000;71:1158-1166.
66. Sugawara S, Shibazaki M, Takada H, et al. Contrasting effects of an aminobisphosphonate, a potent inhibitor of bone resorptions, on lipopolysaccharide-induced production of interleukin-1 and tumor necrosis factor alpha in mice. *Br J Pharmacol.* 1998;125:735-740.
67. Stronski SA, Bettschen-Camin L, Wetterwald A, et al. Bisphosphonates inhibit 1,25-dihydroxyvitamin D3-induced increase of osteocalcin in plasma of rats in vivo and in culture medium of rat calvaria in vitro. *Calcif Tissue Int.* 1988;42:248-254.
68. Reddy MS, Weatherford TW 3rd, Smith CA, et al. Alendronate treatment of naturally-occurring periodontitis in beagle dogs. *J Periodontol.* 1995;66:211-217.
69. Tani-Ishii N, Minamida G, Saitoh D, et al. Inhibitory effects of incadronate on the progression of rat experimental periodontitis by porphyromonas gingivalis infection. *J Periodontol.* 2003;74:603-609.
70. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants.* 2006;21:349-353.
71. Lane N, Armitage GC, Loomer P, et al. Bisphosphonate therapy improves the outcome of conventional periodontal treatment: results of a 12-month, randomized, placebo-controlled study. *J Periodontol.* 2005;76:1113-1122.
72. El-Shinnawi UM, El-Tantawy SI. The effect of alendronate sodium on alveolar bone loss in periodontitis (clinical trial). *J Int Acad Periodontol.* 2003;5:5-10.
73. Takaishi Y, Ikeo T, Miki T, et al. Suppression of alveolar bone resorption by etidronate treatment for periodontal disease: 4- to 5-year follow-up of four patients. *J Int Med Res.* 2003;31:575-584.
74. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. *Bone.* 1996;18:75-85.
75. Ruggiero SL, Mehrotra B, Rosenbert TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg.* 2004:62:527-534.
76. Wade M, Suzuki J. Issues related to diagnosis and treatment of bisphosphonate-induced osteonecrosis of the jaws. *Grand Rounds Oral-Sys Med.* 2007;2:46-53.
77. Hofbauer LC, Khosla S, Dunstan CR, et al. The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption. *J Bone Miner Res.* 2000;15:2-12.

78. Nakashima T, Kobayashi Y, Yamasaki S, et al. Protein expression and functional difference of membrane-bound and soluble receptor activator of NF-KappaB ligand: modulation of the expression by osteotropic factors and cytokines. *Biochem Biophys Res Commun.* 2000;275:768-775.
79. Teng YT, Nguyen H, Gao X, et al. Functional human T-cell immunity and osteoprotegerin ligand control alveolar bone destruction in periodontal infection. *J Clin Invest.* 2000;106: R59-67.
80. Liu D, Xu JK, Figliomeni L, et al. Expression of RANKL and OPG mRNA in periodontal disease: possible involvement in bone destruction. *Int J Mol Med.* 2003;11:17-21.
81. Crotti T, Smith MD, Hirsch R, et al. Receptor activator NF kappaB ligand (RANKL) and osteoprotegerin (OPG) protein expression in periodontitis. *J Periodontal Res.* 2003;38:380-387.
82. Mogi M, Otogoto J, Ota N, et al. Differential expression of RANKL and osteoprotegerin in gingival crevicular fluid of patients with periodontitis. *J Dent Res.* 2004;83:166-169.
83. Jin Q, Cirelli JA, Sugai JV, et al. RANKL inhibition via osteoprotegerin blocks bone loss in experimental periodontitis. *J Dent Res.* 2007;86:in press.
84. Morony S, Capparelli C, Sarosi I, et al. Osteoprotegerin inhibits osteolysis and decreases skeletal tumor burden in syngeneic and nude mouse models of experimental bone metastasis. *Cancer Res.* 2001;61:4432-4436.
85. Zhang J, Dai J, Qi Y, et al. Osteoprotegerin inhibits prostate cancer-induced osteoclastogenesis and prevents prostate tumor growth in the bone. *J Clin Invest.* 2001;107:1235-1244.
86. Capparelli C, Kostenuik PJ, Morony S, et al. Osteoprotegerin prevents and reverses hypercalcemia in a murine model of humoral hypercalcemia of malignancy. *Cancer Res.* 2000;60:783-787.
87. Oyajobi BO, Anderson DM, Traianedes K, et al. Therapeutic efficacy of a soluble receptor activator of nuclear factor KappaB-IgG Fc fusion protein in suppressing bone resorptions and hypercalcemia in a model of humoral hypercalcemia of malignancy. *Cancer Res.* 2001;61:2572-2578.
88. Kong YY, Feige U, Sarosi I, et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature.* 1999;402:304-309.
89. Haynes DR, Crotti TN, Loric M, et al. Osteoprotegerin and receptor activator of nuclear factor kappaB ligand (RANKL) regulate osteoclast formation by cells in the human rheumatoid arthritic joint. *Rheumatology (Oxford).* 2001;40:623-630.
90. Romas E, Sims NA, Hards DK, et al. Osteoprotegerin reduces osteoclast numbers and prevents bone erosion in collagen-induced arthritis. *Am J Pathol.* 2002;161:1419-1427.
91. Haynes DR, Crotti TN, Potter AE, et al. The osteoclastogenic molecules RANKL and RANK are associated with periprosthetic osteolysis. *J Bone Joint Surg Br.* 2001;83:902-911.
92. Kim KJ, Kotake S, Udagawa N, et al. Osteoprotegerin inhibits in vitro mouse osteoclast formation induced by joint fluid from failed total hip arthroplasty. *J Biomed Mater Res.* 2001;58:393-400.
93. Goater JJ, O'Keefe RJ, Rosier, et al. Efficacy of ex vivo OPG gene therapy in preventing wear debris induced osteolysis. *J Orthop Res.* 2002;20:169-173.
94. Bolon B, Carter C, Daris M, et al. Adenoviral delivery of osteoprotegerin ameliorates bone resorption in a mouse ovariectomy model of osteoporosis. *Mol Ther.* 2001;3:197-205.
95. Ulrich-Vinther M, Carmody EE, Goater JJ, et al. Recombinant adeno-associated virus-mediated osteoprotegerin gene therapy inhibits wear debris-induced osteolysis. *J Bone Joint Surg Am.* 2002;84-A:1405-1412.
96. Kostenuik PJ, Bolon B, Morony S, et al. Gene therapy with human recombinant osteoprotegerin reverses established osteopenia in ovariectomized mice. *Bone.* 2004;34:656-664.
97. Bekker PJ, Holloway D, Nakanishi A, et al. The effect of a single dose of osteoprotegerin in postmenopausal women. *J Bone Miner Res.* 2001;16:348-360.
98. Body JJ, Greipp P, Coleman RE, et al. A phase I study of AMGN-0007, a recombinant osteoprotegerin construct, in patients with multiple myeloma or breast carcinoma related bone metastases. *Cancer.* 2003;97:887-892.
99. Lopez-Marcos JF, Garcia-Valle S, Garcia-Iglesias AA. Periodontal aspects in menopausal women undergoing hormone replacement therapy. *Med Oral Patol Oral Cir Bucal.* 2005;10:132-141.
100. Reinhardt RA, Payne JB, Maze CA, et al. Influence of estrogen and osteopenia/osteoporosis on clinical periodontitis in postmenopausal women. *J Periodontol.* 1999;70:823-828.
101. Norderyd OM, Grossi SG, Machtei EE, et al. Periodontal status of women taking postmenopausal estrogen supplementation. *J Periodontol.* 1993:64:957-962.
102. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434-1441.
103. Misof BM, Roschger P, Cosman F, et al. Effects of intermittent parathyroid hormone administration on bone mineralization density in the iliac crest biopsies from patients with osteoporosis: a paired study before and after treatment. *J Clin Endocrinol Metab.* 2003;88:1150-1156.
104. Miller SC, Hunziker J, Mecham M, et al. Intermittent parathyroid hormone administration stimulates bone formation in the mandibles of aged ovariectomized rats. *J Dent Res.* 1997;76:1471-1476.
105. Barros SP, Silva MA, Somerman MJ, et al. Parathyroid hormone protects against periodontitis-associated bone loss. *J Dent Res.* 2003;82:791-795.
106. Padbury AD Jr, Tozum TF, Taba M Jr, et al. The impact of primary hyperparathyroidism on the oral cavity. *J Clin Endocrinol Metab.* 2006;91:3439-3445.
107. Schneider A, Taboas JM, McCauley LK, et al. Skeletal homeostasis in tissue-engineered bone. *J Orthop Res.* 2003;21:859-864.

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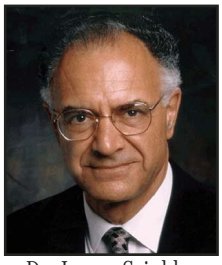
Dr. James Sciubba

A DESTRUCTIVE AND DEADLY POST-EXTRACTION COMPLICATION

By James J. Sciubba, DMD, PhD

Case 2-2007
This is the case of a 69-year-old woman with a rapidly progressive postextraction complication.

Case Presentation
A 69-year-old woman developed a cellulitis over the right mandibular body 4 weeks after routine extraction of the mandibular second molar, which was deeply carious and associated with severe pain. The extraction was performed without difficulty under local anesthesia, with no immediate postoperative complications. Over the ensuing 2 weeks, a modestly tender swelling developed over the right lower third of the face over the extraction site, with pain along the mandibular buccal region. The swelling enlarged in association with mild trismus, a fetid odor, and a low-grade fever.

Medical History
The patient essentially had been well until approximately 10 years earlier, when she was diagnosed with a right neuroretinitis by her ophthalmologist. Shortly thereafter she developed a rheumatologic disorder of unknown etiology, with widespread joint pain and severe fatigue. In an effort to rule out systemic lupus erythematosus and vasculitic disorders such as Wegener's granulomatosis, a laboratory workup was performed; results included a borderline-positive antinuclear antibody level, a nonspecific perinuclear anti-neutrophilic cytoplasmic antibody positivity pattern, and negative myeloperoxidase and proteinase 3 test results as measured by enzyme-linked immunosorbent assay. A suspected myocardial infarction was evaluated with no performance compromise or other abnormalities noted at the time of her initial cardiac workup.

Approximately 18 months prior to being seen by her dentist for right mandibular pain, she was treated with oral glucocorticosteroids[i] for her rheumatologic complaints, with a good response noted. Steroids were discontinued using a slow, tapering dosing schedule over a period of several weeks. Six months later, she was evaluated for elevated Mycoplasma levels on a titer test and for recurrent severe fatigue and joint pain, and was again treated with an oral steroid regimen. After this she was suspected of suffering from Sjögren's syndrome and autoimmune thyroiditis. Serum inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate, were elevated. An earlier echocardiogram had revealed an ejection fraction of 40% to 50%.

During the next several weeks a slow taper of the steroids was initiated. However, a recurrence of severe fatigue and joint pain required reinitiating the steroid dosage at 12.5 mg daily. Further medical workup for celiac sprue, Whipple's disease, and Wegener's granulomatosis was negative, as were results on enteroscopy.

At this point severe pain developed within the right mandible, where a nonrestorable second molar was noted by her dentist (Figure 1). A routine simple extraction of the nonrestorable tooth was performed uneventfully by an oral surgeon. Four days later she developed a right lower facial cellulitis, with a subsequent diagnosis of mandibular osteomyelitis. After the development of facial swelling and cellulitis, she was placed on a series of oral antibiotics and, soon thereafter, a brief course of intravenous antibiotics, including vancomycin and piperacillin/tazobactam. No improvement of the cel-

[i] Prednisone is manufactured by Zenith Goldine Pharmaceuticals, Ft. Lauderdale, FL

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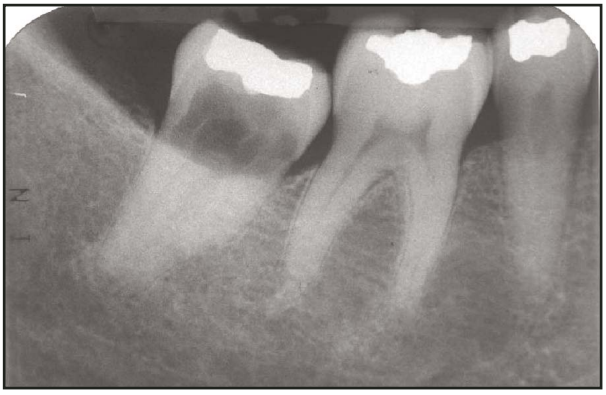

Figure 1

The nonrestorable mandibular second molar tooth, extracted several weeks prior to admission.

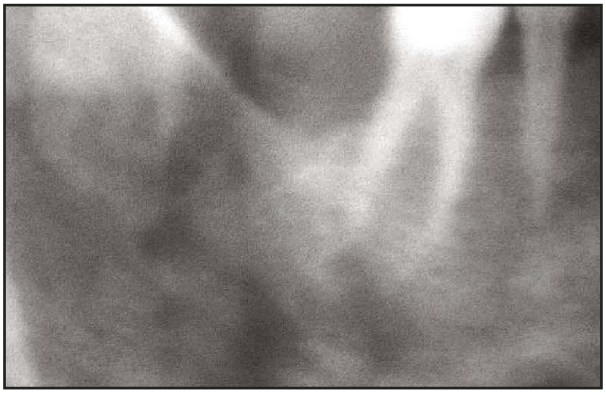

Figure 2

Developing osteomyelitis with mottled medullary bone extending toward the inferior border of the mandible.

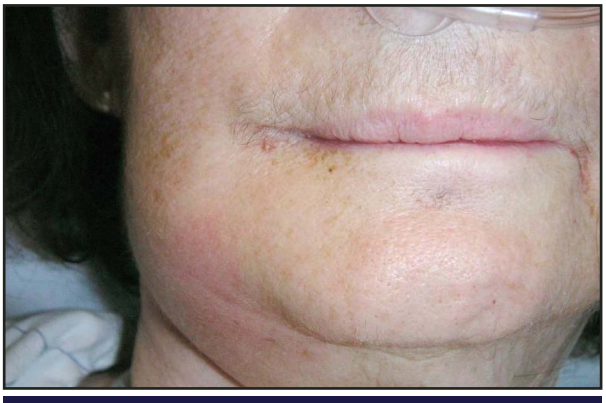

Figure 3

A modest, tender facial asymmetry and associated erythema over the right mandibular body, extending to the submandibular triangle, was noted at the initial in-hospital consultation.

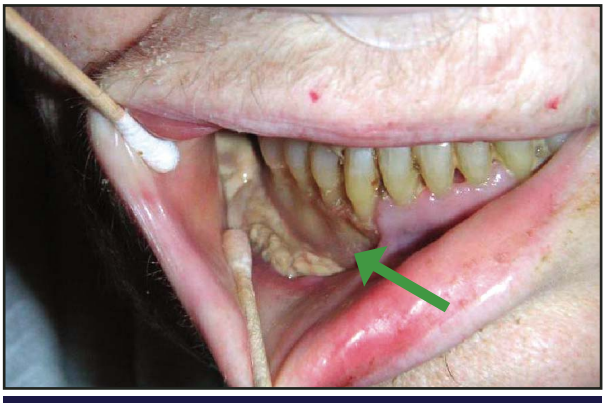

Figure 4

Within the mucobuccal fold is the remnant of fully necrotized mucosal tissue, which had a leathery quality and was avascular and insensate. Exposed buccal alveolar bone extends from the canine region to the extraction site (arrow).

lulitis was noted. A routine panoramic radiograph (Figure 2) demonstrated a mottled area of bone destruction at the extraction site that extended toward the inferior cortical margin of the mandible. She was subsequently hospitalized for management of the persistent oral infection and her general complaints of fatigue. An echocardiogram performed on admission revealed an ejection fraction of 20% to 25%, along with the presence of a large left pleural effusion. The origin of her left ventricular dysfunction was unclear, although the possibility that this was related to her underlying undiagnosed rheumatologic disease was considered. A routine complete blood cell count showed an elevated white blood cell count of 26.5.

The initial oral and head and neck examination in the hospital revealed a mild, diffuse, and slightly tender right facial swelling centered over the mandibular body, with an attendant degree of mild cutaneous erythema and trismus (Figure 3). Intraorally a gray-colored area of necrotic soft tissue was present along the right buccal aspect of the mandible, extending into the mucobuccal fold (Figure 4). The tissue was insensate, densely fibrous and did not bleed upon manipulation. In addition, and of note, the buccal cortical bone in the molar and premolar region was exposed in the absence of suppuration. The adjacent dentition was intact, firm, and without evidence of periodontal disease. The tooth socket at the recent extraction site was open, and the alveolar bone was exposed, with no sign of granulation tissue along the axial walls or at the base of the defect. A polymicrobial infection was sus-

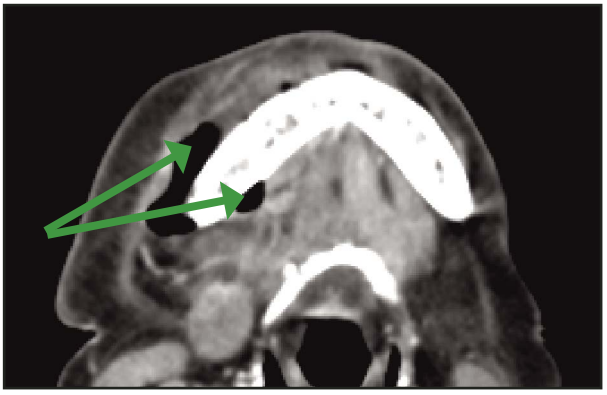

Figure 5

This axial computed tomography scan demonstrates the presence of gas locules (arrows) on either side of the mandibular body, directly adjacent to the area of the earlier dental extraction.

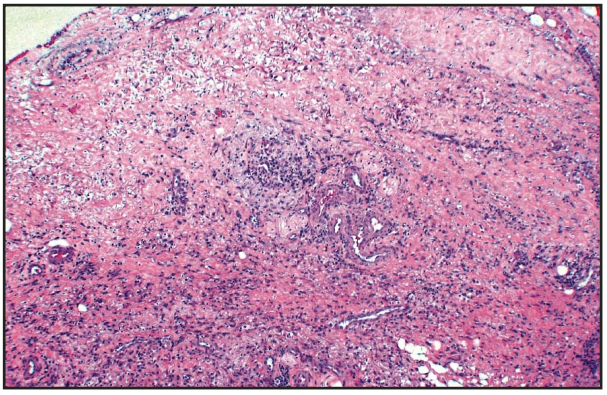

Figure 6

A nonspecific inflammatory infiltrate in association with deep extension into fatty tissues is noted.

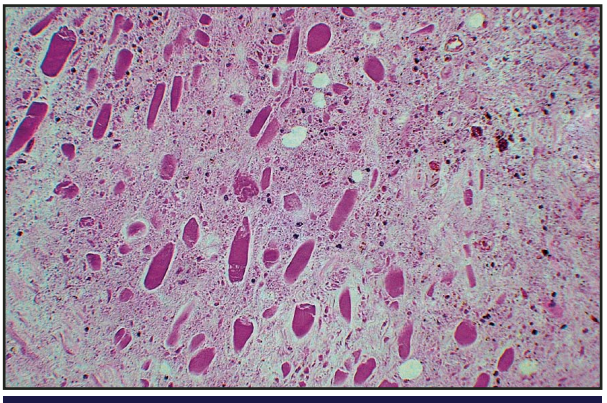

Figure 7

Myonecrosis and muscle bundle separation characterize the deep extent of the necrotizing process.

pected and later confirmed by culture, which identified aerobic, anaerobic, and facultative anaerobic bacteria. This prompted initial treatment with intravenous gatifloxacin and metronidazole, accompanied by parenteral hydration and analgesics. A subsequent bone scan of the mandible indicated findings consistent with osteomyelitis of bacterial origin.

Computed tomography revealed soft tissue swelling within the submandibular and retromandibular areas, with fluid accumulation in association with aggregates of gas within the soft tissues on both the lingual and buccal aspects of the mandible (Figure 5). Extensive cellulitis of the right neck was present, along with hypopharyngeal asymmetry. After the imaging studies, aggressive surgical debridement of the necrotic tissue was performed intraorally and in the anterior neck, followed by pathologic evaluation of the removed tissue.

Pathologic analysis of the submitted tissue demonstrated broad areas of tissue necrosis, bacterial overgrowth, separation of skeletal muscle bundles and nerve trunks, muscle necrosis, and a mixed inflammatory infiltrate (Figures 6 and 7). No fungal organisms were present on special fungal staining. In concert with the clinical, pathologic, and imaging findings, a diagnosis of necrotizing fasciitis was made.

At 17 days after admission, her condition continued to deteriorate in spite of aggressive antibiotic treatment and cardiac and pulmonary support. She developed bilateral pulmonary emboli with an associated sharp increase in leukocyte count, to 88,000/mm.[3] She later became hypotensive, requiring vasopressors in the presence of persistent sepsis, and developed severe bradycardia. She developed pulseless electrical activity and did not respond to appropriate measures to reestablish a heart rate.

At autopsy the diagnosis of multiorgan failure was made secondary to cellulitis/sepsis originating in the right neck and jaw region. The dental infection was deemed to be the initiating event and its progression the cause of death, within the context of undefined rheumatologic disease that required significant and prolonged systemic immunosuppressive treatment.

Discussion

Necrotizing fasciitis is an uncommon, highly lethal, and rapidly developing disease, spreading polymicrobial infection often associated with group A *streptococci* and

several other organisms, including *Clostridium perfringens* and *Streptococcus pyogenes* and the necrotoxins produced therein.[1] On occasion a single organism may produce some necrotizing infections, but in the current case the origin of the infectious process was odontogenic, which is typically polymicrobial or mixed in type. Such mixtures of organisms include aerobic, anaerobic, facultative anaerobic, and obligate anaerobic species.

Although this condition is rare, dental professionals often are the first to encounter it, as most cases of necrotizing fasciitis of the head and neck region are chiefly the result of an odontogenic infectious process, as in the case described here. The use of immunosuppressive drugs (glucocorticosteroids) to manage the ill-defined rheumatologic disease is likely to have contributed to the rapid progress of the infection, but a significant percentage of cases arise in patients who are otherwise well. The mortality rate associated with this disease in patients with attendant systemic conditions was 24.2% in 1 study, but ranges upward from 19.2%; previously healthy patients had a reported 9.3% mortality rate.[2] An assessment of the literature demonstrates a significantly higher percentage of fatal outcomes in patients with attendant systemic disease — particularly diabetes mellitus and alcoholism — than in patients who are otherwise healthy. Poor outcome is also associated with the time that elapses until aggressive surgical debridement, with patients who undergo this procedure within 24 hours having a significantly lower mortality rate (19.6%) than those who deferred surgery for more than 24 hours (50%).[2,3]

Factors responsible for the initiation and progression of tissue damage, in addition to local microbial and host resistance factors, include factors produced by the invading microflora. These include potent necrotoxins and activation of the coagulation system, which in turn leads to formation of thrombi and tissue infarction. Heparinases produced at the infectious site further abet the procoagulative events. Elevations in local hydrostatic pressure further inhibit local vascular perfusion within the area.

Given the polymicrobial nature of the infection, this case is best considered a Type I necrotizing fasciitis. In contrast, where documented *S. pyogenes* (group A *Streptococcus*) is present, Type 2 necrotizing fasciitis is designated, and when clostridial species are isolated, clostridial myonecrosis (gas gangrene) is diagnosed.[4]

This severe life-threatening condition, when affecting the head and neck region, is most commonly associated with an odontogenic infection (apical, periodontal) as the seminal or initiating clinical event. This condition may be mistaken for a more typical odontogenic infection, as its early presentation may not be specific. In addition, the isolated organisms are predominantly β-*hemolytic Streptococci*, *Staphylococcus*, and *Bacteroides* spp., and common resident oral and periodontal pathogens. Diagnostic considerations include the presence of pronounced pain and systemic toxicity (leukocytosis, elevated C-reactive protein levels), the presence of gas within local soft tissues, and identification of tissue breakdown. Underlying immunosuppression and concurrent systemic disease further increase the risk of progression.

Management must be aimed at immediate surgery in an effort to reduce the risk of mortality. It is crucial to remember that dental infection is the main cause of this condition when it occurs in the head and neck area.

Summary

An example of a common odontogenic infection requiring a routine dental extraction is presented within the broader context of an iatrogenically immunocompromised host having an ill-defined rheumatologic disease, with a fatal outcome secondary to a polymicrobial necrotizing infection of odontogenic origin. A broad area and high volume of tissue necrosis was found, with extension well beyond the mandibular site of origin. Clinicians must adequately evaluate immunocompromised patients with regard to potential systemic consequences prior to instituting ambulatory surgical procedures that would normally be considered routine. Finally, once the correct diagnosis is established, immediate and aggressive surgical debridement and supportive management are crucial.

References

1. Chapnick EK, Abter EI. Necrotizing soft tissue infections. *Infect Dis Clin N Am.* 1996;10:835-855.
2. Umeda M, Minamikawa T, Komatsubara H, et al. Necrotizing fasciitis caused by dental infection: a retrospective analysis of 9 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2003;95;283-290.
3. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections: risk factors for mortality and strategies for management. *Ann Surg.* 1996;224:672-683.
4. Urschel JD. Necrotizing soft tissue infection. *Postgrad Med J.* 1999;75:645-649.

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PERIODONTAL DISEASE, BACTEREMIA, AND ORTHOPEDIC SURGERY

Donald P. Callan, DDS†
Richard Evans, MD‡
Charles M. Cobb, DDS, PhD§

Abstract
The current literature in both dentistry and orthopedic surgery indicates a need for better collaboration between dental and medical professionals concerning the management of patients with orthopedic joint replacements. Although rare, joint prosthesis infections that emanate from oral bacteremias are potentially devastating. Prophylactic antibiotic treatment in patients at high risk for systemic complications from oral bacteremia has become the standard of care in dentistry; however, routine antibiotic prophylaxis is not recommended for patients who are not at risk. Given the virulent nature of the microbes associated with inflammatory periodontal disease and the potential for bacteremia, it is recommended that patients be evaluated by a dental professional prior to any elective joint replacement surgery.

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*(A complimentary copy of this article may be downloaded at **www.thesystemiclink.com**.)*

Key Words: Antibiotic prophylaxis, bacteremia, inflammation, orthopedic surgery, periodontal disease, prosthetic joint replacement

Introduction

The total population of the oral microflora of the human mouth has been estimated at 6 billion microbes.[1] This number includes approximately 140 taxonomic groups and 700+ different species, although it is unlikely that any one individual harbors more than 200 species.[2,3] It appears that at least 30 species participate in the inflammatory periodontal diseases, although this is likely an underestimate, as many microbes in the periodontal pocket remain uncultivated and uncharacterized.[4] However, the 30 known species have several factors in common: namely, most are gram-negative and anaerobic, and produce endotoxins and other antigens capable of eliciting a profound host immune response.[5,6]

Given the dense and diverse population of oral microbes, it should not be surprising that dental patients are subjected to periodic episodes of transient bacteremias of oral origins. Numerous reports have identified bacteremia in patients after dental treatment procedures such as extractions,[7] scaling,[8,9] periodontal probing,[10] suture removal,[11] orthodontic treatment,[12] restorative dentistry,[13] and nonsurgical endodontic therapy.[14] In addition, normal everyday activities such as mastication,[15] tooth brushing,[16] and dental flossing[17] have been associated with bacteremia. Both Roberts[18] and Guntheroth[15] have suggested that everyday events are more significant than dental procedures in the production of bacteremia. In fact, Guntheroth[15] has suggested that normal everyday activities may result in bacteremia for 90 hours per month, compared with 6 minutes for the average dental extraction.

Several articles have noted that patients with periodontal disease experience a greater incidence and magnitude of bacteremia than do those with a healthy periodontium.[10,19,20] Indeed, Forner and colleagues[19] report that among patients with chronic periodontitis, the magnitude of bacteremia is directly associated with the level of gingival inflammation (i.e., higher gingival and plaque index scores and a higher num-

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ber of sites with bleeding on probing). Interestingly, the authors found no relationship between probing depth and the magnitude of bacteremia, indicating that active inflammation, not the extent of periodontal attachment loss, is the more important of the 2 variables.

Hujoel and colleagues[21] estimated that the total surface area of diseased and ulcerated periodontal pocket epithelium can range from 8 to 20 cm^2, depending on the severity of periodontal disease. Obviously, epithelium ulcerated to this extent offers ample opportunity for connective tissue invasion by bacteria and/or their endotoxins, leading to bacteremia and endotoxemia. Bacteremia and endotoxemia have been implicated in a variety of systemic responses, such as altered platelet function and increased intravascular clotting, and also in synthesis of prostaglandins.[22] The localized inflammatory event of periodontal disease is also implicated in the systemic inflammatory response, leading to the production of acute-phase proteins by the liver (i.e., C-reactive protein, serum amyloid A, haptoglobin, and fibrinogen).[22-24] All of these systemic responses, in turn, may have varying degrees of impact on systemic diseases, including cardiovascular disease,[22,23] ischemic stroke,[22,23] diabetes,[25] adverse pregnancy outcomes,[26] and possibly dementia and Alzheimer's disease.[27]

Total joint arthroplasty

Periodontal disease may play a role in several systemic conditions, including diabetes, adverse pregnancy outcomes, and clinical problems, such as malnutrition related to masticatory problems, generally associated with older age groups (>65 years).[28] The practice of preventive dentistry has allowed more individuals to retain functional dentition into their elderly years. The paradox of this success is that these same individuals are exposed to the risk of periodontal disease while in an age group that accounts for a large percentage of total joint arthroplasty.[29] In the United States, for example, it is estimated that more than 500,000 total joint arthroplasties are performed annually.[30-32] The majority of such surgeries involve knee and hip joint prostheses in patients 50 years of age or older.[31,33] However, joint replacements in younger patients are being done with increased frequency as total joint component technology advances.

Prosthetic joint infections

Total joint replacement has a 10-year success rate of >90%,[34] yet failures do occur. Infection of a newly positioned joint prosthesis can be a devastating complication, resulting in significant morbidity, pain, loss of function, and possibly total failure requiring surgical revision and long-term antibiotic therapy. Infections involving prosthetic joint replacements are classified as *early* or *late*.[35] Early infections are defined as those occurring within 3 months after implantation surgery and generally result from the introduction of an infectious agent at the time of surgery.

Although the incidence of early periprosthetic sepsis is quite low, on the order of 0.39%,[36] the unreported incidence in the community setting, where most joint replacements are performed, is likely higher. The infection rate is also higher in revision surgery for worn out or failed, but noninfected joint replacements. Overall, the rate of infection for joint prosthetic surgery is generally <2%. One study[36] of 6,489 primary and revision total knee surgeries reported an infection rate of 1.8%.

Late or delayed infections of a total joint arthroplasty occur more than 3 months after surgery and are usually secondary to bacteremia. Interestingly, the incidence of late-occurring infections is also relatively low, generally <1%.[37] The 2 years after prosthetic joint placement are considered to be the most hazardous in terms of potential bacterial seeding of the implant site via the hematogenous route.[38] It has been suggested that enhanced vascularity of the surgical site during the 2 years of wound healing enhances the possibility of hematogenous seeding of bacteria.[39] However, in spite of the potential for infection, several articles have noted that the risk of a joint prosthesis becoming infected from bacteremia of oral origin is exceedingly low.[32, 39-42]

Most joint infections appear to be caused by *Staphylococcus aureus, Staphylococcus epidermidis*, or other coagulase-negative staphylococci.[43] The predominant oral microbes implicated in both endocarditis and septic prosthetic joints belong to the viridans (α-hemolytic) streptococci family (i.e., *Streptococcus mitis, Streptococcus oralis, Streptococcus gordonii, Streptococcus sanguis*, and *Streptococcus mutans*).[39-42] In addition to being α-hemolytic, all of the viridans streptococci are aerobic, gram-positive microbes. Pallasch and Slots[41] analyzed data from 6 studies and determined that roughly 66% of 281 bacteria isolated from prosthetic joint infections were staphylococci, but only 5% were classified as viridans streptococci.

The viridans streptococci and some gram-negative, anaerobic periodontal pathogens express virulence factors that facilitate their ability to promote infection. Such factors include expression of cell-wall adhesion molecules that allow adherence to host cells or the surface of implanted biomedical devices. In addition, both staphylococci and viridans streptococci are capable of complex biofilm formation with a characteristic extracellular matrix that, in turn, promotes microbial colonization and adherence to biomaterial surfaces, renders the biofilm resistant to penetration by antibiotics, and enables evasion of the

host immune response.[43,44] In general, bacteria involved in soft tissue infections are capable of producing leukotoxins and hemolysins, both of which facilitate destruction of host tissues.[43]

It is well established that infection, tissue necrosis, or invasive surgery can be triggering factors that stimulate macrophages, fibroblasts, endothelial cells, and other host cell types to produce and release a variety of inflammatory cytokines.[45] Infection of prosthetic joints may also involve the localized production and release of inflammatory cytokines (e.g., interleukins 1, 6, and 8, and tumor necrosis factor α), prostaglandins, and host-cell enzymes, specifically the matrix metalloproteinases (e.g., collagenase, elastase, and gelatinase), all of which may promote inflammation-mediated destruction of connective tissue and bone.[43-46]

Orthopedic infections resulting from bacteremia of oral origin are rare, yet common sense would seem to dictate that the time, energy, and money spent preventing prosthetic joint infection is likely more effective than that expended in treating an established infected joint.[29] Thus, 3 questions arise: 1) What are the responsibilities of the dentist and orthopedic surgeon regarding prevention of infection before and during surgery? 2) What are the conditions for prescribing antibiotics for prophylaxis and treatment of patients with existing joint prostheses? 3) What are the responsibilities of the dentist and orthopedic surgeon regarding collaborative treatment of patients prior to and after joint replacement?

Collaborative treatment prior to and after joint replacement

The mutual responsibilities of the dentist and orthopedic surgeon are to reduce the incidence of dental bacteremia-related total joint sepsis by providing collaborative antibiotic prophylaxis and treatment of patients requiring joint replacement. Close collaboration regarding both the treatment of existing oral infections prior to joint surgery and the use of antibiotic prophylaxis after placement of a joint prosthesis is crucial for providing optimal care for the orthopedic surgery patient.

Prosthetic total joint infection is a catastrophic surgical complication. Routine surgical clearance to prevent complications from other organ systems is normally required preoperatively and often includes evaluations by subspecialists such as internists and cardiologists. One of the few absolute contraindications to total joint arthroplasty is a pre-existing focus of infection elsewhere.[47] Patient dental history is unreliable, and the orthopedic preoperative checklist historically has not included a documented risk of perioperative dental bacteremia. Prevention of total joint infection from exogenous sources typically receives a great deal of attention, unlike surveillance and correction of endogenous sources of bacteremia. Preoperative collaboration should take the form of a dental evaluation and clearance prior to total joint replacement to minimize this source of sepsis.

Dental clearance can be documented with a simple form that can be sent via facsimile or e-mail by the patient's dentist to the orthopedic surgeon. Patients who have received a complete dental examination within 6 months prior to surgery should easily obtain dental clearance. In the authors' experience, a substantial portion of patients needing joint replacement have not had regular dental care. These patients require dental examination and correction of sources of bacteremia prior to clearance for joint replacement surgery. Occasionally extensive preoperative dental procedures are required for patients who have neglected routine dental care.

For the first postoperative year, antibiotic prophylaxis is recommended prior to all dental manipulations except routine cleanings. After the first year, antibiotic prophylaxis is required only for "high-risk" procedures, such as extraction or root canal, that cause bleeding. Dental-related antibiotic prophylaxis in patients not allergic to penicillin should include cephalexin, cephradine, or amoxicillin in a dose of 2 g given 1 hour prior to the dental procedure. For patients allergic to penicillin, clindamycin 600 g should be given 1 hour prior to the dental procedure.[48,49]

Patients who have received a joint prosthesis should be seen on a regular basis for routine dental care. It is well known that periodontal disease is related to bacteremia that may feature a wide variety of microbes, both aerobic and anaerobic. Thus, to reduce the risk of bacteremia of oral origin, patients with an orthopedic prosthesis should be free of inflammatory periodontal disease. To ensure the least possible risk for the patient, the dentist and orthopedic surgeon should maintain an open line of communication, with each clinician emphasizing to the patient the importance of good oral hygiene and dental care. Although infection from periodontal pathogens may be rare, the occurrence of an infected prosthetic joint can have a devastating impact on the patient.

Prior to scheduling any joint replacement surgery, the patient should be examined to assess periodontal health, and appropriate treatment completed as necessary. The orthopedic physician must have a working knowledge of periodontal diseases, their diagnoses, and various modalities of treatment. More specifically, the orthopedic physician must understand that periodontal therapy to control oral bacterial loads and inflammation can require either surgical or nonsurgical treatment, may involve systemic or localized delivery of antibiotics, and is likely to involve

a significant amount of time. Indeed, the treatment of inflammatory periodontal disease requires a minimum of 4 to 6 weeks, and should include intensive patient education to maintain the health of the periodontal tissues. Except for cases of trauma, joint replacement surgery is generally an elective procedure and can usually be delayed until the patient has consulted with a dentist and/or periodontist and completed the treatment required to establish an oral cavity free of infection and inflammation. After completion of periodontal therapy, the dentist/periodontist should document the patient's oral health, including any potential problems, and consult with the orthopedic surgeon before joint replacement surgery is scheduled.

Once joint replacement surgery is approved and scheduled, responsibility then shifts to the surgical staff to prevent surgery-related infection. Guidelines promoted by the Patient Safety Committee of the American Academy of Orthopedic Surgeons[50] have been organized in an "outside-to-in" concept of environmental control that includes the operating room environment, the patient environment, and the wound environment.

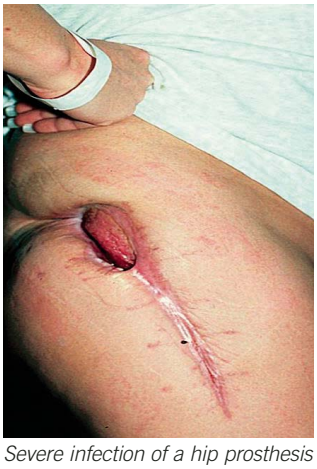
Guidelines for the operating room environment include maintaining positive air pressure in the conventional operating room, with more than 15 volume exchanges per hour.[50] Despite decades of experience with clean-air operating rooms, no uniform methods for efficiently preventing infections have been developed. However, laminar flow statistically reduces airborne contamination, and body exhaust suits, in combination with other infection control measures, also appear to improve infection rates. Use of scrubs, masks, and gloves and sterilization of all surgical instruments should follow published guidelines. Ethylene oxide has been classified as a carcinogen and is being replaced by H_2O_2 sterilization procedures. Operating room doors should remain closed and needless traffic, activity, and personnel eliminated. Strict adherence to operating room discipline and Universal Precautions should be maintained. Hand washing with soap and water is highly effective in preventing nosocomial spread of organisms. Newer alcohol and chlorhexidine gluconate-based hand lotions appear to provide more effective antisepsis than standard scrub and are recommended in the absence of visible soiling. In addition, healthcare personnel are more likely to comply with hand hygiene procedures if surgeons, senior medical staff, and peers are seen to be compliant.

Maintaining the optimal patient environment includes monitoring and maintenance of normal glycemia, normothermia, and administration of antimicrobial prophylaxis.[50] The initial dose of the appropriate antimicrobial should be given within 1 hour preceding incision, and repeated during surgery as needed to maintain blood levels. Antimicrobial prophylaxis should be ceased within 24 hours, even if catheters or drains are still in place. Protection of the wound environment includes hair removal with an electric shaver or depilatory (not a safety razor) just prior to surgery, and proper skin preparation of the surgical field with alcohol, povidones, iodophors, or chlorhexidine gluconate. As much as possible, operative time should be minimized, tissue handled gently, and dead space and tissue eradicated. Whether to drain to reduce the risk of hematoma is questionable, because it raises concern regarding tract drainage, creates a potential passageway for infection, and increases transfusion requirements. There is no evidence that antibiotic irrigation is effective in prophylaxis for infection in orthopedic procedures.

Antibiotic prophylaxis and treatment in patients with joint prostheses

Dentistry has successfully implemented, and accepted as the standard of care, the recommendations of the American Heart Association[51] that antibiotic prophylaxis be provided for those patients at risk of developing adverse systemic problems as a result of bacteremia caused by oral tissue manipulation. In at-risk heart patients, the low incidence of complications from dental procedure-related bacteremia is the result of good communication among patients, cardiologists, and dentists.

Figure 1



Severe infection of a hip prosthesis occurring several years after placement as a result of bacteremia. Based on patient's dental history, the bacteremia had a high probability of oral origin.

The problem of antimicrobial prophylaxis in orthopedic implant surgery will become increasingly important and complex as the general population ages and requires more arthroplasty procedures. Given the low rate of prosthetic joint infection from bacteremia of oral origin and the fact that such bacteremia is transient and, for most dental procedures, of low magnitude,[19] one must conclude that the prescribing of prophylactic antibiotics for patients with an existing joint prosthesis is based on anecdotal, historical, and legal concerns. However, infection, should it occur, can be devastating to the patient and require additional surgeries, lengthy recovery time, and additional medical expenses (Figure 1). Despite this, some authors have proposed that the risk of adverse reaction to the antibiotic prophylaxis is greater than the risk of infection.[39,52-55] Statistically, it has been estimated that 30 of every 100,000 patients

Table 1: Guidelines for prophylactic antibiotics in patients at increased risk of hematogenous total joint infection

Patients at High Risk for Total Joint Infection, for Whom Antibiotic Prophylaxis is Recommended

- All patients during the first 2 years after prosthetic joint replacement
- Patients who are immunocompromised or immunosuppressed, as a result of the following:
  - Inflammatory arthropathies (e.g., rheumatoid arthritis, systemic lupus erythematosus)
  - Drug-induced immunosuppression
  - Radiation-induced immunosuppression
- Patients with the following comorbidities:
  - History of previous prosthetic joint infection
  - Malnourishment
  - Hemophilia
  - Human immunodeficiency virus infection
  - Insulin-dependent diabetes (Type I)
  - Malignancy

undergoing total joint replacement experience a late infection requiring treatment; by contrast, if all 100,000 patients were prescribed prophylactic antibiotics, 40 cases of anaphylaxis and 4 deaths would be incurred.[52]

In spite of such statistical observations, the American Dental Association (ADA) and the American Academy of Orthopedic Surgeons (AAOS) have published antibiotic prophylaxis guidelines.[48] Furthermore, the AAOS and the American Urological Association (AUA) performed a thorough review of all available data to determine the need for antibiotic prophylaxis to prevent hematogenous prosthetic joint infections in urological patients who have undergone total joint arthroplasties. Similar to the advisory statement issued jointly by the AAOS and ADA, the AAOS and AUA issued an advisory statement[49] that has been adopted by both organizations. The guidelines do not recommend the routine use of antibiotic prophylaxis for most dental patients with total joint arthroplasty. Instead, antibiotic prophylaxis is considered for selected at-risk patients (Table 1).[48] In making the decision to provide antibiotic prophylaxis prior to dental treatment in patients with an existing joint prosthesis, the clinician must accurately assess the level of oral disease, type of treatment required (See Table 2 entitled *Stratified Risk for Bacteremia, by Dental Procedure,*[48] which may be accessed and downloaded from the *Clinical Decision-Making Tools* section at www.thesystemiclink.com), risk of bacteremia, potential risk of prosthesis-related infection, associated secondary risk factors (e.g., diabetes, immunocompromised status, obesity, and smoking),[36] type of antibiotic indicated (See Table 3 entitled *Suggested Antibiotic Prophylaxis Regimens,*[48] which may be accessed and downloaded from the *Clinical Decision-Making Tools* section at www.thesystemiclink.com) and its spectrum of action, and the potential for adverse side effects. Applications of these guidelines are not part of the orthopedic surgeon's skill set. Orthopedic surgeons must rely on dental assessment and application of these guidelines to prevent total joint infections from oral bacteremia.

In addition, the clinician must be aware of the potential for bacteremia resulting from untreated oral disease. Ching and colleagues[56] have reported 4 cases of late infection of joint prostheses with *Streptococcus viridans* in patients with poor oral health. An additional 4 cases, reported by Bartzokas and colleagues,[57] involved *S. sanguis*-mediated late joint infections in patients with documented oral sepsis and poor oral hygiene. The evident implication of this small series of case reports is that prevention and/or treatment of oral disease and good oral hygiene are a requisite of good orthopedic surgery and dental practice. Performing total joint arthroplasty only in patients without chronic dental bacteremia is good practice, as is preventing dental procedure-related bacteremia in patients with existing total joint prostheses.

Conclusion

The current literature in both dentistry and orthopedic surgery indicates a need for better collaboration between dental and medical professionals concerning the management of patients with orthopedic joint replacements. Although rare, joint prosthesis infections that emanate from oral bacteremias are potentially devastating to patients and can result in failure of the prosthesis and the need for revision surgery. Antibiotic prophylaxis of patients at high risk for systemic complications from oral bacteremia has become the standard of care for dentistry and appears to be a satisfactory approach to management of such patients; however, routine antibiotic prophylaxis is not recommended for patients who are not at risk. Given the virulent nature of the microbes associated with inflammatory periodontal disease and the potential for bacteremia, it is recommended that patients be evaluated by a dental professional prior to any elective joint replacement surgery. The collaborative effort between the dental professional and the orthopedic surgeon should continue subsequent to joint replacement surgery, as an ongoing measure to promote proper healing. Further research is needed to verify the severity and frequency of joint replacement infections caused by oral bacteremias, and to determine the degree of protective benefit derived from antibiotic prophylaxis.

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References

1. Nuckolls GH, Slavkin HC. Paths of glorious proteases. *Nat Genet*. 1999;23:378-380.
2. Aas JA, Paster BJ, Stokes LN, et al. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol*. 2005;43:5721-5732.
3. Paster BJ, Olsen I, Aas JA, et al. The breadth of bacterial diversity in the human periodontal pocket and other sites. *Periodontol 2000*. 2006;42:80-87.
4. Kroes I, Lepp PW, Relman DA. Bacterial diversity within the human subgingival crevice. *Proc Natl Acad Sci USA*. 1999;96:14547-14552.
5. Zambon JJ. Periodontal diseases: microbial factors. *Ann Periodontol*. 1996;1:879-925.
6. Offenbacher S. Periodontal diseases: pathogenesis. *Ann Periodontol*. 1996;1:821-878.
7. Rajasuo A, Perkki K, Nyfors S, et al. Bacteremia following surgical dental extraction with an emphasis on anaerobic strains. *J Dent Res*. 2004;83:170-174.
8. Kinane DF, Riggio MP, Walker KF, et al. Bacteremia following periodontal procedures. *J Clin Periodontol*. 2005;32:708-713.
9. Waki MY, Jolkovsky DL, Otomo-Corgel J, et al. Effects of subgingival irrigation on bacteremia following scaling and root planing. *J Periodontol*. 1990;61:405-411.
10. Daly CG, Mitchell DH, Highfield JE, et al. Bacteremia due to periodontal probing: a clinical and microbiological investigation. *J Periodontol*. 2001;72:210-214.
11. Giglio JA, Rowland RW, Dalton HP, et al. Suture removal-induced bacteremia: a possible endocarditis risk. *J Am Dent Assoc*. 1992;123:65-66, 69-70.
12. Lucas VS, Omar J, Vieira A, et al. The relationship between odontogenic bacteremia and orthodontic procedures. *Eur J Orthodont*. 2002;24:293-301.
13. Roberts GJ, Holzel HS, Sury MR, et al. Dental bacteremia in children. *Pediat Cardiol*. 1997;18:24-27.
14. Savarrio L, MacKenzie D, Riggio M, et al. Detection of bacteremias during non-surgical root canal treatment. *J Dent*. 2005;33:293-303.
15. Guntheroth WG. How important are dental procedures as a cause of infective endocarditis? *Am J Cardiol*. 1984;54:797-801.
16. Bhanji S, Williams B, Sheller B, et al. Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. *Pediat Dent*. 2002;24:295-299.
17. Lineberger LT, De Marco TJ. Evaluation of transient bacteremia following routine periodontal procedures. *J Periodontol*. 1973;44:757-762.
18. Roberts GJ. Dentists are innocent! "Everyday" bacteremia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. *Pediatr Cardiol*. 1999;20:317-325.
19. Forner L, Larsen T, Kilian M, et al. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. *J Clin Periodontol*. 2006;33:401-407.
20. Takai S, Kuriyama T, Yanagisawa M, et al. Incidence and bacteriology of bacteremia associated with various oral and maxillofacial surgical procedures. *Oral Surg Oral Med Oral Path Endod*. 2005;99:292-298.
21. Hujoel PP, White BA, Garcia RI, et al. The dentogingival epithelial surface area revisited. *J Periodontal Res*. 2001;36:48-55.
22. De Nardin E. The role of inflammatory and immunological mediators in periodontitis and cardiovascular disease. *Ann Periodontol*. 2001;6:30-40.
23. Gapski R, Cobb CM. Chronic inflammatory periodontal disease: a risk factor for cardiovascular disease and ischemic stroke? *Grand Rounds Oral-Sys Med*. 2006;1:14-22.
24. Loos BG. Systemic markers of inflammation in periodontitis. *J Periodontol*. 2005;76:2106-2115.
25. Moritz AJ, Mealey BL. Periodontal disease, insulin resistance, and diabetes mellitus: a review and clinical implications. *Grand Rounds Oral-Sys Med*. 2006;2:13-20.
26. Paquette DW. Periodontal disease and the risk for adverse pregnancy outcomes. *Grand Rounds Oral-Sys Med*. 2006;4:14-24.
27. Stein PS, Scheff S, Dawson DR III. Alzheimer's disease and periodontal disease: mechanisms underlying a potential bi-directional relationship. *Grand Rounds Oral-Sys Med*. 2006;3:14-24.
28. Iacopino AM. Maintaining oral health in the aging population: the importance of the periodontal-systemic connection in the elderly. *Grand Rounds Oral-Sys Med*. 2006;3:25-37.
29. Marculescu CE, Osmon DR. Antibiotic prophylaxis in orthopedic prosthetic surgery. *Infect Dis Clin North Am*. 2005;19:931-946.
30. Mendenhall S. Hip and knee implant review. *Orthop Network News*. 1997;8:1-16.
31. Curry S, Phillips H. Joint arthroplasty, dental treatment, and antibiotics; a review. *J Arthroplasty*. 2002;17:111-113.
32. Barry JM, Ferguson CD. Current dental concepts in antibiotic prophylaxis for total joint replacement patients. *Gen Dent*. 2000;48:170-172.
33. Deacon JM, Pagliaro AJ, Zelicof SB, et al. Prophylactic use of antibiotics for procedures after total joint replacement. *J Bone Joint Surg Am*. 1996;78:1755-1770.
34. American Academy of Orthopedic Surgeons. *National Center of Health Statistics*. Rosemont, Illinois: American Academy of Orthopedic Surgeons; 1999.
35. McPherson EJ, Woodson C, Holtom P, et al. Periprosthetic total hip infection. *Clin Orthop Relat Res*. 2002;403:8-15.
36. Peersman G, Laskin R, Davis J, et al. Infection in total knee replacements: a retrospective view of 6,489 total knee re-

placements. *Clin Orthop Relat Res*. 2001;392:15-23.
37. Saleh KJ, Macaulay A, Radosevich DM, et al. The Knee Society Index of Severity for failed total knee arthroplasty: development and validation. *Clin Orthop Relat Res*. 2001;392:153-165.
38. Seymour RA, Whitworth JM, Martin M. Antibiotic prophylaxis for patients with joint prosthesis — still a dilemma for dental practitioners. *Brit Dent J*. 2003;194:649-653.
39. Portnof JE, Israel HA, Brause BD, et al. Dental premedication protocols for patients with knee and hip prostheses. *NY State Dent J*. 2006;72:20-25.
40. Hanssen AD, Osmon DR, Nelson CL. Prevention of deep prosthetic joint infection. *J Bone Joint Surg*. 1996;78-A:458-471.
41. Pallasch TJ, Slots J. Antibiotic prophylaxis and the medically compromised patient. *Periodontol 2000*. 1996;10:107-138.
42. Kingston R, Kiely P, McElwain JP. Antibiotic prophylaxis for dental or urological procedures following hip or knee replacement. *J Infect*. 2002;45:243-245.
43. Shirtliff ME, Mader JT. Acute septic arthritis. *Clin Microbiol Rev*. 2002;15:527-544.
44. Berendt AR, McLardy-Smith P. Prosthetic joint infection. *Curr Infect Dis Rep*. 1999;1:267-272.
45. Ebersole JL, Cappelli D. Acute-phase reactants in infections and inflammatory diseases. *Periodontol 2000*. 2000;23:19-49.
46. Janeway CA, Travers P, Walport M, et al. T-cell mediated immunity. In: *Immunobiology: The Immune System in Health and Disease*, 5th Ed. New York, NY: Garland Publishing; 2001: 295-333.
47. NIH Consensus Development Conference on Total Knee Replacement, National Institutes of Health Consensus Development Conference Statement, December 8-10, 2003.
48. American Dental Association, American Academy of Orthopedic Surgeons. Antibiotic prophylaxis for dental patients with total joint replacements. *J Am Dent Assoc*. 2003;134:895-899.
49. American Academy of Orthopaedic Surgeons and American Association of Orthopaedic Surgeons. Advisory statement: Antibiotic Prophylaxis for Urological Patients with Total Joint Replacements. Available at: http://www.aaos.org/about/papers/advistmt/1023.asp. Accessed Feb 28, 2007.
50. Clyburn TA, Evans RP, Holtom PD, et al. Current trends and hot topics in infection prevention, treatment, and surveillance. Scientific exhibit #SE71 presented by AAOS Infections Committee at American Academy of Oral Surgery 74th Annual Session; February 14-18, 2007; San Diego, CA.
51. Dajani AED, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *J Am Med Assoc*.1997;277:1794-1801.
52. Scott JF, Morgan D, Avent M, et al. Patients with artificial joints: do they need antibiotic cover for dental treatment? *Aust Dent J*. 2005;50:S45-S5.
53. Seymour RA, Whitworth JM. Antibiotic prophylaxis for endocarditis, prosthetic joints, and surgery. *Dent Clin North Am*. 2002;46:635-651.
54. Jacobson JJ, Schweitzer S, DePorter DJ, et al. Antibiotic prophylaxis for dental patients with joint prostheses: a decision analysis. *Int J Technol Assess Health Care*. 1990;6:569-587.
55. Jacobson JJ, Schweitzer S, Kowalski CJ. Chemoprophylaxis of prosthetic joint patients during dental treatment: a decision-utility analysis. *Oral Surg Oral Med Oral Pathol*. 1991;72:167-177.
56. Ching DW, Gould IM, Rennie JA, et al. Prevention of late haematogenous infection in major prosthetic joints. *J Antimicrob Chemother*. 1989;23:676-680.
57. Bartzokas CA, Johnson R, Jane M, et al. Relation between mouth and haematogenous infections in total joint replacement. *BMJ*. 1994;309:506-508.

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THE IMPORTANCE OF MEDICAL-DENTAL COLLABORATION IN BISPHOSPHONATE THERAPY

This report chronicles a case involving bisphosphonate-induced osteonecrosis (BION) which has helped me better appreciate the importance of coordinated treatment between dentistry and medicine.

The patient is a 57-year-old female, whose past medical history was significant for hypothyroidism, high cholesterol, and breast cancer, which was first diagnosed in 1999. She subsequently underwent standard surgery, postoperative radiation, and chemotherapy treatments. In 2002, she was found to have metastatic disease involving the liver, lung, and possibly bone. She was then managed with another course of chemotherapy including intravenous zoledronic acid and glucocorticosteroids. In 2005, her cancer spread to her brain where she required additional radiation treatment. Currently, her medications also include levothyroxine, lovestatin, and lapitinib. Her zoledronic acid has been modified to bi-monthly infusions.

Her past dental history revealed risk factors for developing BION of the jaw. In early 2002, we referred this patient to a periodontist for moderate generalized periodontitis. Pocket depths ranged from 4 to 8 mm with teeth #14 and #30 being most affected. The patient elected to postpone the recommended surgical treatment because she was dealing with the reoccurrence of cancer at this time. Our office kept her on a 3-month periodontal recall in order to maintain optimal oral health while she underwent further cancer therapies. Her oral hygiene and tissue health have fluctuated as her immune system was taxed by the chemotherapy. A recall visit in July 2005 revealed increased inflammation both mesially and palatally of tooth #14, which were locally treated. At her October 2005 visit, there was profuse bleeding upon probing and an 8 mm pocket on the mesial of tooth #14 and the palatal tissue now appeared to be developing a fistula. The patient reported that an August 2005 bone scan revealed enhanced uptake in her left maxilla at which time the oncologist temporarily discontinued her zoledronic acid therapy and recommended a dental evaluation. The patient was referred to an oral surgeon who noted erythema along the palatal tissue of tooth #15, with slight tenderness. No bone exposure or swelling was noted at this time. Periapical films revealed normal trabecular patterns and no periapical radiolucencies. A working diagnosis of acute apical periodontitis was made. Invasive oral surgery was not recommended because of her zoledronic acid use and increased risk of BION. The oral surgeon advised frequent hygiene recare visits and immediately referred the patient to an endodontist for retreatment of an existing root canal performed on the mesial buccal of tooth #14 in December 2005. Tooth #15 was not treated. A tissue check in late December 2005 showed local improvement and stability except for some continued inflammation around tooth #14.

The patient presented for a routine recare visit in February 2006 and stated that she had been placed back on zoledronic acid at an infusion interval of 2 months, and that she had undergone additional radiation treatment for her brain metastasis. A more recent bone scan in December 2005 revealed further metastatic lesions at the base of her brain. Her only complaint at this time was a bumpy feel to her upper left hard palate. Oral examination revealed an oval shaped dehiscence measuring 7 mm in length and 3-5 mm in width, 4 mm medial to the gingival margin of teeth #14 and #15. The patient was referred to an oral surgeon.

In late March 2006, she was reexamined by the oral surgeon who noted asymptomatic exposed palatal bone in the left

posterior maxilla. The area was free of acute infection and BION was suspected. Close monitoring was advised, as well as regimens of excellent oral hygiene and frequent hygiene recalls. The patient postponed her April recall appointment, and presented back in May 2006 with an increase in the bone exposure which had tripled in size from what was noted 3 months earlier. The surrounding tissue was edematous, spreading through the interproximal to the buccal tissue of teeth #14 and #15. These teeth were mobile; the exposed bone was loose and easily removed with a curette. The palatal roots of these teeth were fully exposed. The patient was referred back to the oral surgeon, who noted healthy granulation tissue throughout the site and the area free of acute infection. The patient was placed on twice daily chlorhexidine gluconate (CHG) rinses and the surgeon reiterated the need for conservative dental treatment and only superficial scaling while this area healed. The patient's late July 2006 recall visit noted improved healing with no complications.

By September 2006, the patient's health had declined. Her hearing was reduced in both ears and she was quite unsteady, using canes to ambulate. She was trying a new chemotherapeutic agent but no other changes in her medical history were noted. Tooth #14 still exhibited a mesial pocket; profuse bleeding upon probing was noted. Another area beginning to dehisce palatal to tooth #3, which appeared as a magenta colored dimple and felt firm to palpation.

At her next 2-month recare appointment in November 2006, there was unilateral swelling to the left side of her face, including a severely swollen upper lip, class 2-3 mobility of the left maxillary teeth, and severe halitosis. Numerous buccal fistulas with suppuration were also noted in this quadrant, extending from tooth #9 to #15. Upon discussing these findings with her home health aide, it was discovered that 1 month prior the patient had presented to her physician for a similar facial swelling. Her primary care physician diagnosed the swelling as acute angioedema caused by a food allergy, overlooking the possibility of an odontogenic infection. Her physician did not refer the patient to her dentist but immediately referred the patient back to the oral surgeon where a diagnosis of an acute canine space odontogenic infection was made and the patient was placed on amoxicillin/clavulante postassium 875 mg bid and subsequently treated with incision and drainage soon after. At a 2-week follow up, the patient showed good healing and was placed on long-term, low dose amoxicillin/clavulante postassium 500mg bid. A tissue check in late December 2006 revealed that the fistulas resolved and tooth mobility significantly improved. The patient was without complaint and placed on a 4-week recare schedule.

At her most recent visit at the end of January 2007, continued healing of the upper left quadrant with much less mobility was observed. The patient was able to fully function with all of her teeth at that time. The right palatal dehiscence was once again observed and the exposed bone measured approximately 2x2 mm. There was also another dimpled area developing just posterior to this site. The patient continued with amoxicillin/clavulante postassium and CHG rinses twice daily. Her oral hygiene was very good.

This case made it necessary to collaborate with other healthcare professionals to improve my understanding of the patient's medical needs. I conferred with this patient's home health aide, nurse practitioner at her oncologist's office, oral surgeon, and her primary care physician. As a result, I feel that I am now a part of her healthcare team. Her nurse practitioner shared with me that I was the first dental hygienist she had collaborated with on case management.

I firmly believe that dental evaluation prior to starting bisphosphonate therapy, discussing the possibility of BION with patients, and the importance of very short recare intervals to minimize or prevent or reduce the risk of developing BION, should be the standard protocol. A 3-month recall has been the standard, but I have learned that significant change can take place within this time. I also believe that an oncology patient's medical team and dental team must bilaterally share information regarding diagnostic changes to better manage the overall health of the patient.

In summary, I feel that the increasing incidence of BION can be a catalyst for opening the lines of communication between medicine and dentistry, and provides an excellent opportunity to stress the importance of the oral-systemic link in the care of my patients.

Acknowledgment
I would like to acknowledge Dr. Peter Albanese for his help in formatting this case study.

Original Article

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OSTEOPOROSIS PREVENTION AND SCREENING: POTENTIAL ROLE FOR HEALTHCARE PROFESSIONALS?

Joyce Horn, RDH, BS, MS†
Anthony M. Iacopino, DMD, PhD‡

Abstract
Long-term inflammation is associated with irreversible destruction of parenchyma and connective tissues. Osteoporosis and periodontitis are examples of chronic inflammatory diseases that cause significant damage to soft and hard tissues, and recent evidence suggests potential links between these diseases. Periodontitis may be an early marker for osteoporosis. It is also possible that osteoporosis increases the risk of development or progression of periodontitis as the result of reduced quantity and quality of alveolar bone. Thus, preventive approaches, especially transdisciplinary interventions involving multiple health professionals, may be particularly important for maintaining oral health in individuals with osteoporosis. The collaborative potential of dental hygienists for implementing practical interventions aimed at controlling and preventing chronic diseases has yet to be fully realized. This article reviews current evidence supporting the association of osteoporosis with the onset and progression of periodontal disease and discusses the implications of 2 pilot projects involving the interaction of dental hygienists with the nursing and medical professions as part of the comprehensive healthcare team. As a primarily prevention-oriented healthcare professional, the dental hygienist may be the ideal primary care provider to initiate educational discussions with female patients at risk of osteoporosis, refer for medical evaluation, and follow-up on subsequent oral health appointments. The nature of the dental hygiene curriculum also facilitates collaborative education and clinical training programs that support transdisciplinary wellness approaches to improving oral-systemic health. These pilot projects may serve as a valuable litmus test for innovative models that integrate healthcare education and training with clinical practice to improve overall patient management.

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Key Words: Osteoporosis, risk assessment, periodontal disease, transdisciplinary management, screening

Introduction

Risk assessment and prevention will play an increasingly important role in health care as we gain greater understanding of the bidirectional relationships of chronic conditions. The emerging science of oral-systemic medicine seeks to define these associations and implement this knowledge in patient intervention strategies. Compelling research confirms the prevalence and serious risks of oral diseases among Americans, showing how vitally important good oral health is to general health and well-being.[1] This growing body of evidence supporting connections between periodontal disease and chronic disease risk or exacerbation, provides an opportunity for dental hygienists to engage in transdisciplinary practice with their nurse counterparts.[2-10]

Two recent pilot projects illustrate the potential benefits of this model in the ongoing management of patients with osteoporosis. The *Dental Hygienists' Osteoporosis Educational Intervention* study affiliated with the Pennsylvania Dental Hygienists' Association (J. Gleber, electronic communication to J. Horn, Feb 2007) and the *Oral-Systemic Risk Assessment*

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Rounds pilot clinical training rotations project, developed by the University of New Mexico's Division of Dental Hygiene Graduate Program (J. Horn and A. Scott, 2005), are demonstrating increased efficiency and improved patient care through the integration of various educational, training, and practice activities. Despite the increased awareness of the potential of medical-dental collaboration and calls for demonstration projects that show the utility of dental hygienist–nurse models of care, there continues to be a lack of acceptance and a reluctance to change traditional healthcare models. This is not unusual for the healthcare industry, which is an industry characterized by resistance to innovation.[11-13] This notorious lack of flexibility threatens to delay important current health promotion initiatives arising out of oral-systemic medicine, including the use of dental hygienist-nurse screening programs and early intervention strategies to reduce risks and mitigate systemic disease outcomes.

Chronic conditions are health problems which require ongoing management over a period of years or decades and constitute the major cause of death and disability worldwide. Intervention of these chronic diseases dramatically impacts the demands for healthcare.[14,15] Some of the diseases in the noncommunicable category, such as obesity, diabetes, and cardiovascular disease, overlap, share modifiable risk factors, and have bidirectional relationships linked by the common denominator of chronic inflammation or frustrated repair. Periodontitis has been associated with a number of these systemic conditions, and there are data to suggest that there is also a relationship between periodontitis and osteoporosis.[1,16-19] Our greater understanding of the complexity of caring for patients with these interrelated diseases and conditions and associated comorbidity challenges the roles and responsibilities of individual clinicians, medical groups, insurers, and public health departments.[20,21] Indeed, the evolving body of evidence that supports the plausibility of interrelationships between periodontal diseases and systemic diseases and conditions provides a strong rationale for including the diagnosis and treatment of oral infections as an integral part of comprehensive disease management. Erecting barriers to this type of innovative practice obstructs the use of the available science and evidence base and affects every aspect of healthcare delivery.

The disease of osteoporosis presents an opportunity for medical-dental collaboration. The compelling rationale for collaboration between nurses and dental hygienists in screening for osteoporosis and oral diseases focuses on 3 clusters of influence that correlate with how quickly change will occur: perceptions of an innovation, characteristics of the people who adopt the innovation or fail to do so, and contextual factors involving communication, incentives, leadership, and management.[11,12] Our current system of delivery of care that is overly focused on acute, episodic care begs disruption of the status quo.[12,13]

Osteoporosis and periodontitis

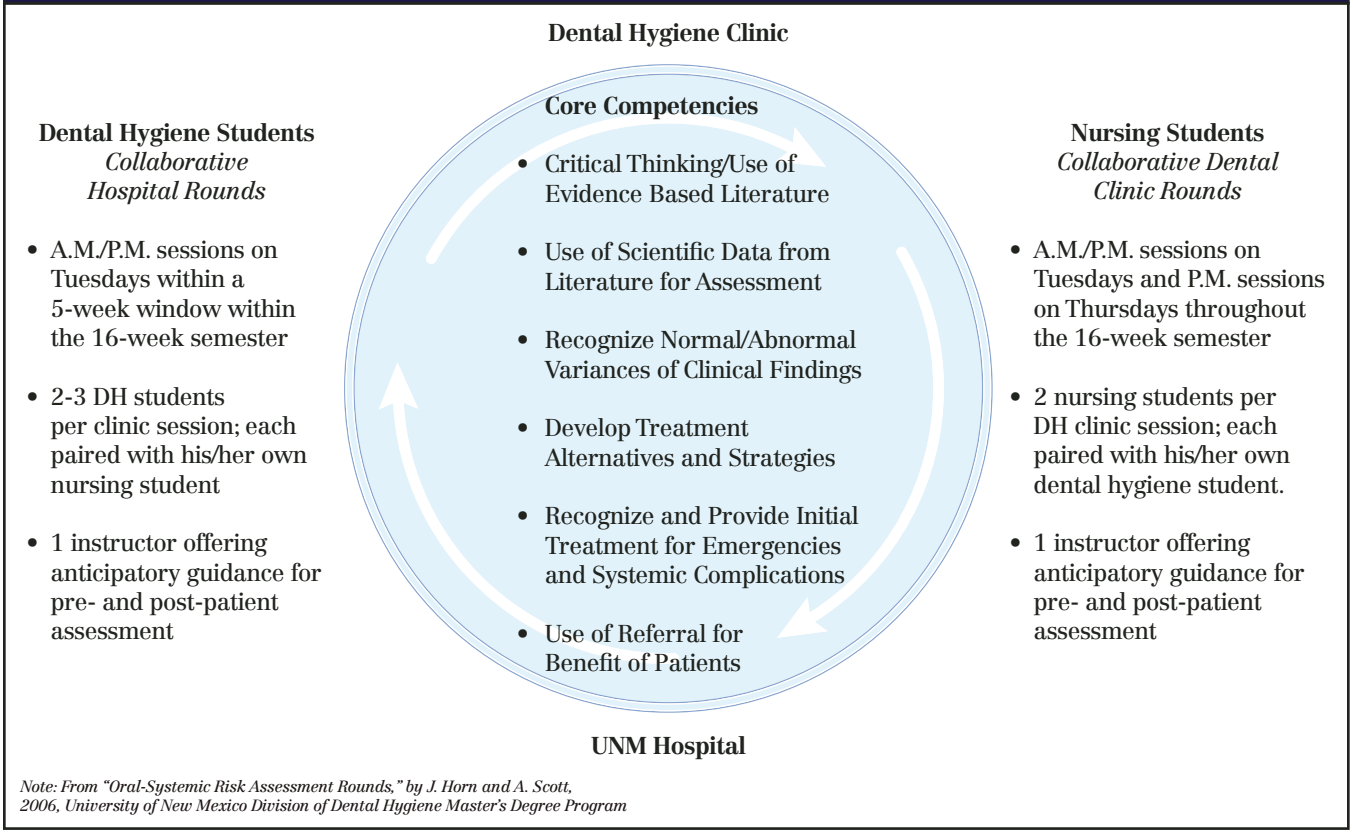
Osteoporosis increases in incidence with advancing age and affects more than 200 million persons worldwide.[22] In the United States (U.S.) alone, 34 million persons are at risk and 10 million already have the disease; 80% of the affected individuals are women. Osteoporosis is characterized by decreased bone mass and poor bone quality, which leads to increased numbers of hip, spine, and wrist fractures.[22] Bone density is expressed as grams of mineral per area or volume and, in any given individual, is determined by peak bone mass and amount of bone loss.[23] Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures), and mineralization.[24] The acute and long-term medical expenses associated with fracture are estimated to be $10-$18 billion.[25,26] The prevalence of osteoporosis and osteoporotic-related fractures is projected to increase significantly unless the underlying bone health status of Americans is significantly improved.[20] By 2010, roughly 12 million people over the age of 50 are expected to have osteoporosis and another 40 million to have low bone mass.[27] By 2020, those figures are expected to jump to 14 million cases of osteoporosis and more than 47 million cases of low bone mass.[27]

The American Academy of Orthopedic Surgeons and the National Osteoporosis Foundation's joint position paper[22] supports the belief that patient and health profession educational programs are essential for reducing osteoporotic fractures. These educational programs should include information about:

- *Associated risk factors, including insufficient calcium intake, sedentary lifestyle, smoking, excessive alcohol consumption, family history of fractures, small or slender body frame, fair skin, and white or Asian background*
- *Early diagnosis of osteoporosis, which is usually made by using a combination of a complete medical history/physical examination, skeletal radiographs, bone densitometry, and bone turnover tests*
- *The importance of adequate dietary intake of calcium, vitamin D, and other nutrients at an early age, especially in young girls*
- *The efficacy and safety of estrogen and estrogen antagonists, bisphosphonates, calcitonin, and evolving hormone therapies to prevent and treat osteoporosis*
- *Sufficient exercise and activity*
- *Fall prevention strategies*

Periodontitis affects 75% of the American public and is currently defined as an infection-mediated destruction of the supporting structures of the tooth, alveolar bone,

Figure 1: Educational programming model to stimulate dental hygiene-nursing collaboration



Note: From "Oral-Systemic Risk Assessment Rounds," by J. Horn and A. Scott, 2006, University of New Mexico Division of Dental Hygiene Master's Degree Program

periodontal ligament, and gingival tissues.[28] Periodontitis is responsible for most of the tooth loss in adult populations, which usually begins before the age of 20. The primary etiological bacteria which have been implicated include *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, and *Actinobacillus actinomycetemcomitans*.[29] Periodontal disease is characterized by a host response elicited by bacteria and bacterial biproducts that diffuse through the epithelium and initiate an inflammatory response.[30,31] Studies[16,17] indicate that this oral disease has more than a casual relation with serum lipids and proinflammatory cytokines, inducing negative effects on systemic health. Potential mechanisms by which host factors may directly or indirectly influence the onset and progression of periodontal disease in patients with osteopenia include low bone density in the oral cavity, bone loss as an inflammatory response to infection, genetic susceptibility, and shared exposure to risk factors.[18,32] The risk factors for periodontal disease that can be used by nurses and other healthcare professionals in screening are listed in Table 2 entitled *Assessment of Risk Factors for Periodontal Disease*,[33] which may be accessed and downloaded from the *Clinical Decision-Making Tools* section at www.thesystemiclink.com.

Epidemiologic studies suggest a reciprocal influence of osteoporosis and periodontal disease.[19] Both diseases are chronic, multifactorial diseases that share common risk factors and bone tissue damage characteristics. Some studies[20] have shown that periodontitis could be an independent risk factor for several systemic diseases and conditions, including osteoporosis. Several recent studies[29] have attempted to define the relation between osteoporosis and periodontitis by using clinical attachment level, alveolar crestal height, tooth loss, and mandibular bone density as assessment criteria. Periodontitis and oral bone loss evaluations include radiographic measures of alveolar bone height and residual ridge resorption, probing depths to measure clinical attachment loss, and documentation of tooth loss. Oral bone density studies measure absolute bone density with techniques such as dual photon absorptiometry, quantitative computed tomography, and radiographic absorptiometry. Studies also approximate change in bone density over time with computer-assisted densitometric image analysis. Studies have generally supported a positive association between periodontitis and osteoporosis; however, several factors, such as small sample sizes, variable methods, and lack of standardized techniques, prevent definitive conclusions.[21]

Table 1
Red flags that warrant further assessment for osteoporosis or other bone diseases

- History of fractures related to mild or moderate trauma
- Family history of bone disease
- Low body weight
- Weight loss of more than 1% per year in the elderly
- Late onset of sexual development
- Unusual cessation of menstrual periods
- Anorexia nervosa
- Athletic amenorrhea syndrome
- Patients being treated with drugs that affect bone metabolism (e.g., glucocorticoids)
- Patients with diseases linked to secondary osteoporosis
- High levels of serum calcium or alkaline phosphatase in otherwise healthy patients
- Hyperparathyroidism, hyperthyroidism, or treatment with high doses of thyroid hormone
- Height loss or progressive spinal curvature

Note: From *Bone Health and Osteoporosis: A Report of the Surgeon General* (Chapter 8), by R.H. Carmona, 2004, U.S. Department of Health and Human Services.

Time for a new model for chronic disease management — transdisciplinary care

According to the World Health Organization, current systems of healthcare share similar characteristics regarding chronic, noncommunicable diseases: they are organized to provide acute illness care, the patient's role in management is not emphasized, follow-up is sporadic, community services tend to be ignored, and preventive interventions are underutilized.[15] The importance of identifying novel and improved approaches to meet the healthcare needs of all Americans is emphasized in the 2004 U.S. Surgeon General's report[20] on bone health and osteoporosis. This report not only reflects the burden to society and individuals, but also addresses the obstacles healthcare providers face when attempting to change practice patterns through transdisciplinary models of healthcare delivery.

Examples of transdisciplinary dental hygiene models for education and patient care

Dental Hygienists Osteoporosis Educational Intervention Study

A pilot study entitled *Dental Hygienists' Osteoporosis Educational Intervention*, initiated through an educational grant to the Pennsylvania Dental Hygienists' Association, began in November 2005 with 75 dental hygiene students from the 3 academic programs in Pennsylvania (J. Gleber, electronic communication to J. Horn, Feb 2007). The pilot study seeks to validate that dental hygienists can play an active role in the education and screening of patients at increased risk for osteoporosis. Dental hygiene students received 4 hours of education from physicians related to the incidence, etiology, progression, and prevention of osteoporosis. Additionally, the dental hygiene students received training on patient communication. The goal of this part of the project is to enable the dental hygiene students to improve their understanding of the risk factors associated with osteoporosis and which bone-healthy behaviors can be adopted to maintain or improve bone health. This information is being communicated to the students' female patients as part of a comprehensive healthcare model.

To test the validity of this model, these dental hygiene students are using osteoporosis screening and education protocols in their clinics. Women above the age of 50 are asked to complete a pre-osteoporosis intervention questionnaire for baseline assessment of their knowledge of osteoporosis and self-management of the disease. These patients are then provided a tri-fold educational brochure with a risk factor screening questionnaire which they are also asked to complete. Dental hygiene students review this information with patients during subsequent visits at which time patients are also provided specific information on adopting healthy bone behaviors, such as increased calcium intake and weight-bearing exercises. Patients who are determined to be at high risk are referred to physicians. Health history findings that trigger the need for further assessment for osteoporosis or other bone diseases are listed in Table 1. Patients are telephoned approximately 3 months after their dental hygiene visit for a follow-up phone interview which lasts 5-6 minutes, during which time the patients are asked about any changes in bone health or lifestyle and whether they followed through with recommended evaluation for osteoporosis with their physicians.

Oral-Systemic Risk Assessment Rounds pilot project

The Division of Dental Hygiene, College of Nursing, and the University of New Mexico Hospital at the University of New Mexico are currently participating in a pilot project called *Oral-Systemic Risk Assessment Rounds* which is designed to enhance direct patient care while educating nursing and dental hygiene students on how to take a collaborative approach to wellness promotion (J. Horn, written communication, April 2006). An overview of the entire oral-systemic risk assessment training program is given in Figure 1. Recognizing the lack of interaction between dental hygienists and nurses, the pilot's foremost goal is to raise awareness of the importance of oral health.

Through dual learning and problem-solving strategies, interdisciplinary initiatives which utilize oral-systemic risk assessment evaluation, and bilateral point-of-care extramural rotations, the pilot project seeks to promote interdisciplinary training and develop protocols for improving oral-systemic health.

The Division of Dental Hygiene is organizationally housed within the Department of Surgery, School of Medicine at the University of New Mexico. It is unique in that it is the only dental hygiene program in the U.S. housed within a medical school. This creates many opportunities for interdisciplinary education and practice. The nature of the dental hygiene curriculum also facilitates collaborative education and clinical training programs that support transdisciplinary wellness approaches that improve oral-systemic health. The diversified education and training experiences facilitate face-to-face interaction and transdisciplinary learning and practice. This pilot program may serve as a valuable litmus test for innovative models that integrate healthcare education and training with clinical practice to improve overall patient management.

Conclusion

Age-related, chronic degenerative diseases are widespread shifting the burden of care toward chronic disease management. Comprehensive healthcare plans have evolved to meet this demand. Usually requiring long-term management, both osteoporosis and periodontitis impose devastating effects on quality of life resulting in tooth loss, reduced facial esthetics, disability, deformity, pain and fractures. Osteoporosis and periodontitis remain under-recognized and under-treated. This significant public health issue demands a transdisciplinary approach which enlists all healthcare providers in screening for periodontal disease and all dental providers screening for osteoporosis.

Clinicians deal with the concept of risk on a daily basis in terms of assessment of oral-systemic diseases, outcomes and therapies. Critical clinical decisions hinge on our interpretation of these risks. To realize quality care, every component of the patient's health must be considered in assessment, prevention, and treatment. In contrast with the primary care provider centered model, a transdisciplinary approach allows for interventions which recognize the inflammatory links which appear to underpin a relationship between periodontal diseases and systemic injury. Continuing cross-disciplinary education and introducing the concept for shared responsibility for whole body wellness will be a catalyst for change.

Osteoporosis is often a silent disease in women after menopause and may be developing in women who appear to be in good health. As a primarily prevention-oriented healthcare professional, the dental hygienist may be the ideal primary care provider to introduce and maintain educational discussions with female patients at risk for osteoporosis, to refer for medical evaluation, and follow-up on subsequent oral health appointments. Regular 6-month appointments with the dental hygienist for preventive oral health care would be a logical time to implement an osteoporosis educational and screening intervention. Through a focus on partnering, the previously described pilot programs illustrate transdisciplinary communication and interaction between health professionals that will contribute greater collaboration between dental hygienists, nurses, physicians, and patients. Transdisciplinary approaches may fill the gaps in health care; especially for potentially related diseases/conditions such as osteoporosis and periodontitis.

References

1. Scannapieco FA. Systemic effects of periodontal diseases. *Dent Clin North Am.* 2005;49:533-550.
2. Nathe C. Dental hygiene's interdisciplinary relationship with dental public health: a position paper. *Int J Dent Hyg.* 2003;1:98-100.
3. Nathe C. Dental hygiene's historical roots in modern-day issues. *Contemp Oral Hyg*. 2003;3:24-25.
4. McCallin A. Interdisciplinary practice-a matter of teamwork: an integrated literature review. *J Clin Nurs.* 2001;10:419-428.
5. Coleman P. Opportunities for nursing-dental collaboration: addressing oral health needs among the elderly. *Nurs Outlook*. 2005;53:33-39.
6. Hein C. Strategies for dental hygienist and nurse collaboration in targeting periodontal and cardiovascular diseases. *Grand Rounds Oral-Sys Med.* 2006;1:36-49.
7. Hein C, Small D. Combating diabetes, obesity, periodontal disease and interrelated inflammatory conditions with a syndemic approach. *Grand Rounds Oral-Sys Med.* 2006;2:36-47.
8. Coleman P, Hein C, Gurenlian J. The promise of transdisciplinary nurse-dental hygienist collaboration in achieving health-related quality of life for elderly nursing home residents. *Grand Rounds Oral-Sys Med.* 2006;3:40-49.
9. Witt JS, Williams KB, Kelly PJ. Engaging hygienists, nurses and social service professionals in an interdisciplinary model for prevention and early care of oral diseases in women of childbearing age. *Grand Rounds Oral-Sys Med.* 2006;4:40-48.
10. McClure D, Essary D, Gurenlian J. A collaborative team approach for symptom management for head and neck cancer patients. *Grand Rounds Oral-Sys Med.* 2007;1:43-51.
11. Berwick DM. Disseminating innovations in health care. *JAMA*. 2003;289:1969-1975.
12. Herzlinger RE. Why innovation in health care is so hard. *Harv Bus Rev.* 2006;84:85-66,156.

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13. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Available at: http://www.nap.edu/books/0309072808/html/. Accessed Jan 6, 2007.
14. Steinberg, K. Wellness in every stage of life: a new paradigm for public health programs. Available at: http://www.cdc.gov/pcd/issues/2007/jan/06_0120.htm Accessed Feb 1, 2007.
15. World Health Organization. Chronic conditions: the global burden. Available at: http://www.who.int/chronic_conditions/systems/en/print.html/. Accessed Feb 1, 2007.
16. Iacopino AM, Cutler CW. Pathophysiological relationships between periodontitis and systemic disease: recent concepts involving serum lipids. *J Periodontol*. 2000;71:1375-1384.
17. Cutler C, Iacopino AM. Periodontal disease: links with serum lipid/ triglyceride levels? Review and new data. *J Int Acad Periodontol*. 2003;5:47-51.
18. Wactawski-Wende J. Oral disease and osteoporosis. *Sci Am*. Available at: http://www.dentalcare.com/soap/products/pdfs/owbh_07.pdf. Accessed Apr 27, 2007.
19. Oh T, Bashutski J, Giannobile W. The interrelationship between osteoporosis and oral bone loss. *Grand Rounds Oral-Sys Med*. 2007;2:10-21.
20. U.S. Department of Health and Human Services. Bone health and osteoporosis: a report of the surgeon general. Available at: http://www.surgeongeneral.gov/library/bonehealth/content.html/. Accessed Dec 15, 2006.
21. Cyzman D, Bour N, McLaury R, et al. Retooling an osteoporosis prevention program to serve low-income populations: a practical guide to bone health. Available at: http://www.cdc.gov/pcd/issues/2005/apr/04_0142s.htm. Accessed Dec 15, 2006.
22. American Academy of Orthopedic Surgeons, American Association of Orthopedic Surgeons. Osteoporosis as a national public health priority. A joint position statement of the American Academy of Orthopedic Surgeons and the National Osteoporosis Foundation. Revised 1999. Available at: http://www.aaos.org/about/papers/position/1113.asp. Accessed Feb 6, 2007.
23. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285:785-795.
24. NIH Consensus Development Program. Osteoporosis prevention, diagnosis, and therapy. NIH Consensus Statement Online 2000 March 27-29;17:1-36. Available at: http://consensus.nih.gov/2000/2000Osteoporosis111html.htm. Accessed Jan 25, 2007.
25. Riggs BL, Melton LJ 3rd. The prevention and treatment of osteoporosis. *New Engl J Med*. 1992;327:620-627.
26. Buist D, LaCroix AZ, Brenneman SK, et al. A population-based osteoporosis screening program: who does not participate, and what are the consequences? *J Am Geriatr Soc*. 2004;52:1130-1137.
27. Mazanec D. Osteoporosis screening; time to take responsibility. *Arch Intern Med*. 2004:164;1047-1048.
28. Albandar JM, Brunelle JA, Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1998-1994. *J Periodontol*. 1999;70:13-29.
29. Wactawski-Wende J. Periodontal diseases and osteoporosis: association and mechanisms. *Ann Periodontol*. 2001;6:197-208.
30. Löesche W, Lopatin DE. Interaction between periodontal disease, medical diseases, and immunity in the older individual. *Periodontol 2000*. 1998;16:80-105.
31. Trowbridge HO, Emling RC. *Inflammation: A Review of the Process*. 5th ed. Illinois: Quintessence;1997.
32. Whalen JP, Krook L. Periodontal disease as the early manifestation of osteoporosis. *Nutr*. 1996;12:53-54.
33. Hein, C. Oral-systemic medicine: a vision to redefine our role within the healing arts-part II. Course lectures presented at: 2006 RDH Under One Roof; July 27, 2006; Las Vegas, NV.

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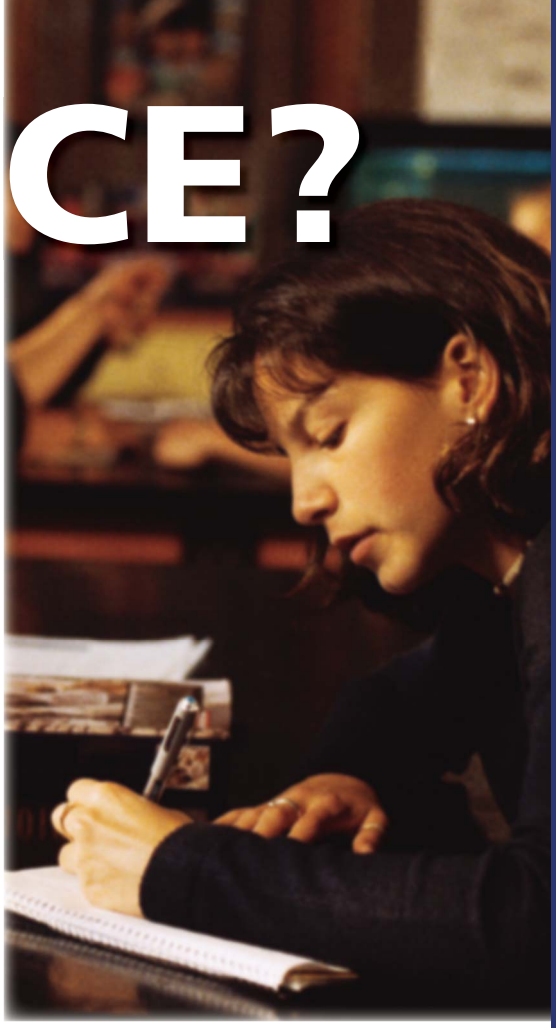

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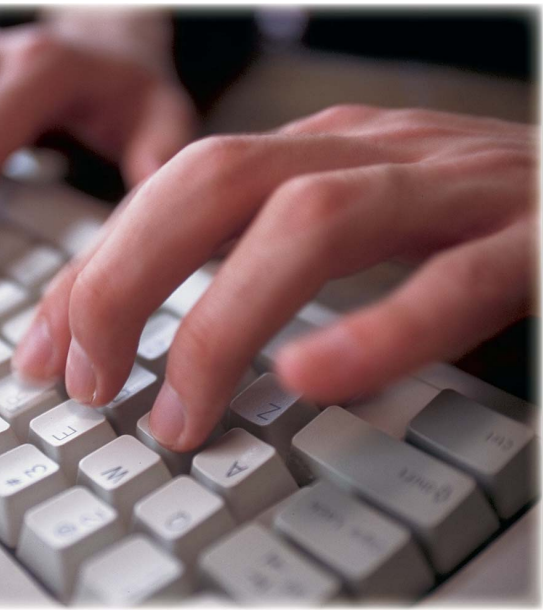

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1. Which of the following are true for both osteoporosis and periodontitis?
- ❑[a] bone resorptive diseases mediated by proinflammatory cytokines
- ❑[b] dependent on host genetics and response
- ❑[c] multifactorial etiology
- ❑[d] predominantly affects older populations
- ❑[e] all of the above

2. Which of the following is not true for osteoporosis?
- ❑[a] more prevalent in postmenopausal women
- ❑[b] affects more than 10 million people in the United States
- ❑[c] risk factors do not include medications or other systemic conditions
- ❑[d] characterized by reduced bone strength, decreased bone mineral density
- ❑[e] all of the above

3. Which of the following is not true for implant therapy in patients with osteoporosis?
- ❑[a] osseointegration of implants in osteoporotic bone is possible
- ❑[b] long-term stability of implants may be compromised
- ❑[c] dental implants are not a viable treatment option for patients with osteoporosis
- ❑[d] there have been reported implant failures in patients with osteoporosis
- ❑[e] all of the above

4. Comprehensive care and bi-directional management of patients with osteoporosis and periodontal disease may include which of the following?
- ❑[a] clinical protocols that minimize further deterioration of systemic or oral bony structures
- ❑[b] intraoral radiography as a screening tool for osteoporosis
- ❑[c] placing patients with osteoporosis into “high risk” periodontitis maintenance and recall
- ❑[d] closely monitoring for signs of osteonecrosis in patients taking bisphosphonates
- ❑[e] all of the above

5. Current approaches to treating systemic/oral bone loss with chemotherapeutics do not include which of the following?
- ❑[a] anti-resorptive agents
- ❑[b] anabolic agents
- ❑[c] bisphosphonates
- ❑[d] stimulating bone resorption and inhibiting bone formation
- ❑[e] all of the above

6. Which of the following is not true of bisphosphonates?
- ❑[a] inhibit bone resorption through multiple mechanisms
- ❑[b] major biological effects are on osteoclasts
- ❑[c] they should not be used in patients with osteoporosis
- ❑[d] there have been reports of significant side effects such as osteonecrosis of the jaw
- ❑[e] all of the above

7. Which of the following is true about the relationship between osteoporosis and periodontitis?
- ❑[a] periodontitis may be an early marker for osteoporosis
- ❑[b] osteoporosis elevates the risk for bone loss in patients with periodontitis
- ❑[c] dental health professionals should screen for periodontitis in patients with osteoporosis
- ❑[d] dental professionals should screen for osteoporosis in post-menopausal women with periodontitis
- ❑[e] all of the above

8. Recent studies investigating the link between osteoporosis and periodontitis have demonstrated:
- ❑[a] no correlation between systemic bone mineral density and tooth loss
- ❑[b] a relationship between periodontal attachment loss and systemic bone mineral density
- ❑[c] clear-cut definitive causal relationships between the diseases
- ❑[d] a correlation between severe vertebral compression and alveolar bone loss
- ❑[e] no association between any aspect of either disease

9. Which of the following is true regarding estrogen?
- ❑[a] withdrawal leads to accelerated bone formation
- ❑[b] increases osteoclast activity
- ❑[c] oral bone loss has never been linked to estrogen-deficient states
- ❑[d] functions to maintain bone mass
- ❑[e] all of the above

10. Risk factors for osteoporosis include which of the following?
- ❑[a] alcohol consumption
- ❑[b] smoking
- ❑[c] physical activity
- ❑[d] calcium intake
- ❑[e] all of the above

Questions are based on a manuscript by Joyce Horn, RDH, BS, MS, and Anthony M. Iacopino, DMD, PhD, entitled "Osteoporosis Prevention and Screening: Potential Role for Oral Health Professionals?"

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CIGNA WEIGHS IN ON ORAL-SYSTEMIC MEDICINE

When evaluating the connection between oral health and overall health, it helps to separate the known and the unknown. Recent studies continue to demonstrate a connection between oral health and overall health.[1] These studies have shown that periodontal disease is connected to preterm birth, diabetes, cardiovascular disease, and other health complications. While this connection has been confirmed through research, it is still unknown among many employers and consumers. Therefore, as a dental insurance plan it becomes important for us to make that connection for our customers so that they too realize how their oral health can affect the rest of their bodies.

As part of this task, CIGNA has created several programs which address this connection. In addition to educating members, these programs remove cost as a barrier to receiving treatment for periodontal disease. For example, CIGNA's Dental Oral Health Integration Program (OHIP) turns evidence into action with its industry-leading benefit enhancements for members who are pregnant or may be suffering from diabetes and/or cardiovascular disease.

Through this program, CIGNA has enabled integrated care between its dental and medical plans in an effort to improve outcomes and reduce dollars spent on high risk medical conditions. Eligible members with CIGNA medical and dental coverage may receive 100 percent reimbursement of their co-pay or coinsurance for certain dental care services, like periodontal scaling and root planing and periodontal maintenance.

For the maternity component of this program, CIGNA leverages its Healthy Babies® program. As part of this program, medical plan members receive a comprehensive kit of information and resources to help them have a healthy pregnancy. They have access to nurses who reinforce the importance of dental care, including routine dental cleanings. The soon-to-be mother is educated on how better oral hygiene is connected to healthier pregnancy outcomes. Research supporting this connection was published in the *Journal of Periodontology's* August 2003 issue.[2] Engaging and educating members to obtain the proper dental treatment, and reimbursing them for certain treatments received during pregnancy, can help avoid the potential emotional and financial impacts associated with preterm births.

In addition, long-term clinical observations detail the relationship between oral health and diabetes. In fact, patients with diabetes may have a more difficult time controlling their blood sugar levels, which could also make it more difficult for them to heal and maintain a healthy lifestyle. This wound healing delay, which many diabetic patients suffer from, could cause an increased risk of systemic illness and result in more extensive, possibly life-threatening complications.

Further research also points to a relationship between periodontal disease and heart disease. Bacteria and bacterial byproducts from the periodontal tissues have been found in the heart and valves of the heart, resulting in serious medical conditions. If circulated in the bloodstream, these bacteria may cause blood clots in the heart and brain, potentially leading to strokes and/or death. By reducing bacterial byproducts in the oral cavity through root planing and scaling procedures, one can reduce the potential negative effects on cardiac conditions.

Fortunately, CIGNA Dental is able to leverage the clinical capabilities of the CIGNA HealthCare disease management program for diabetes and heart disease. Program nurses and case managers can identify those at-risk and communicate the importance of appropriate dental care.

CIGNA Dental is also committed to early detection of oral cancer and added coverage for brush biopsy to all of its dental plans in January 2006. Oral cancer is the sixth deadliest cancer in America. In addition, oral cancer is particularly dangerous because it has a high risk of producing second, primary tumors.[3] As a result, patients who survive a first encounter with the disease have up to a 20 times higher risk of developing a second cancer. By using the brush biopsy procedure to evaluate questionable lesions or spots, cancerous or precancerous lesions can be diagnosed at a very early, highly-curable stage.

Most recently, CIGNA Dental has begun evaluating the integration of benefits related to periodontal disease and osteoporosis, specifically their relationship to oral bone disease. In August 1999, the *Journal of Periodontology* published a study concluding that estrogen supplementation in women within 5 years of menopause slowed the progression of periodontal disease.[4] This, in turn, protected the teeth from developing oral bone disease. Confirming these findings, further studies done by the University of Buffalo found that most people diagnosed with periodontal disease may be at a higher risk of underlying osteoporosis.[5] This results in a strong relationship between the advanced form of gum disease that causes bone loss, gum attachment loss, tooth loss, and osteoporosis.

Fortunately, screening and detection are possible through the use of routine dental radiographs. CIGNA Dental plans provide for diagnostic services, such as bitewing and periapical radiographs. A panorex radiograph is also allowed for diagnostic purposes.

To stay on top of emerging research and trends in oral health integration, CIGNA established a clinical advisory panel consisting of well-known leaders and researchers in the dental profession. Their scientific knowledge and input helps us continue to create and deliver innovative coverage options that address medical/dental integration, as well as new and developing dental technologies.

CIGNA also provides a medical claims integration credit for new clients who package CIGNA medical and dental plans. The credit is a percentage of their claims and may increase when CIGNA's disease management programs for diabetes and heart disease are added. Similar credits may also be applied to existing accounts that add a CIGNA medical or dental plan. This credit serves as an extra incentive for our customers to make that connection between oral health and overall health and also help their employees make oral health a priority, because dental disease accounts for over 164 million lost work hours each year.[1] By educating and encouraging members to obtain routine, preventive care and dental treatments recommended by their dentists, CIGNA hopes to improve health outcomes, which in turn increases productivity for employers.

In summary, we know from recent research that a compelling link exists between oral health and overall health. As a multi-line carrier, CIGNA can clinically integrate its plans in an effort to create and implement programs that engage members in their own health improvement. By promoting and removing cost barriers to dental care, CIGNA Dental is working to increase member access to care, while raising awareness of the importance of oral health.

References

1. US Surgeon General's Report, 2000. Available at: http://www.surgeongeneral.gov/topics/oralhealth/nationalcalltoaction.htm. Accessed Apr 4, 2007.
2. Jeffcoat MK, Hauth JC, Geurs NC, et al. Periodontal disease and preterm birth: results of a pilot intervention study. *J Periodontology*. 2003;74:1214-1218.
3. The Oral Cancer Foundation. Available at: http://www.oralcancerfoundation.org/facts/index.htm. Accessed Apr 4, 2007.
4. Reinhardt RA, Patne JB, Maze CA, et al. Influence of estrogen and osteopenia/osteoporosis on clinical periodontitis in postmenopausal women. *J Periodontology*. 1999;70:823-828.
5. Wactawski-Wende J, Genco RJ. Factors affecting bone metabolism leading to osteoporosis, periodontitis, and tooth loss in postmenopausal women: NHANES III. Meeting of the American Association for the Advancement of Science. February. Philadelphia, PA.

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ISSUES RELATED TO DIAGNOSIS AND TREATMENT OF BISPHOSPHONATE-INDUCED OSTEONECROSIS OF THE JAWS

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Abstract
Bisphosphonate medications, used primarily to treat cancer patients and those with osteoporosis, have been linked to osteonecrosis of the jaws. Patients are considered to have bisphosphonate-induced osteonecrosis of the jaws (BIONJ) if they are being or have been treated with a bisphosphonate, have exposed bone in the maxillofacial region that has persisted for more than 8 weeks, and have no history of radiation therapy to the jaws. Patients may present with pain, swelling and discharge, an area of exposed bone, mobile teeth, they may have more subtle complaints, such as a feeling of heaviness in the jaw or numbness. Treatment generally consists of antibiotic and antifungal agents, and oral hygiene must be diligently maintained. However, BIONJ, especially in the advanced stages, may be refractory to treatment, and surgical debridement and resection may be necessary to alleviate pain and eliminate infection. Because of the widespread use of bisphosphonate medications, medical and dental professionals must be able to knowledgably advise their patients concerning the serious potential side effect of treatment, and all treating clinicians must work diligently together to coordinate care. Well-designed studies are needed to establish treatment protocols.

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*(A complimentary copy of this article may be downloaded at **www.thesystemiclink.com**.)*

Key Words: Avascular necrosis, bisphosphonate, jaw, osteonecrosis, osteoporosis, bone cancer

Introduction

With increasing frequency, dentists are making complex diagnostic decisions for their patients who take bisphosphonate medications, which are linked to osteonecrosis of the jaws. The scientific literature presents conflicting information regarding the impact of bisphosphonate-induced osteonecrosis of the jaws (BIONJ) in medicine and dentistry. Articles range from those that express doubt about the role of bisphosphonates as a cause for BIONJ[1] or attempt to prove a lack of impact on surgical procedures,[2] to those suggesting formal treatment protocols.[3–5] At least 1 textbook is devoted entirely to the issue of BIONJ.[6]

Compounding the confusion is the medicolegal environment surrounding BIONJ. A simple Internet search yields a dozen or more solicitations directed toward patients who have been treated with bisphosphonates, especially the oral forms, alendronate and risedronate. One of the authors of this article (MLW) has even received a solicitation from a law office that included a pamphlet for the author to give to patients who might be interested in pursuing litigation.[7]

In this environment of misinformation and litigation anxiety, it is paramount that dental and medical caregivers have a clear understanding of the development, clinical presentation, and treatment of BIONJ. This article will review these issues in an effort to provide clinicians with adequate information on which to base treatment decisions.

Definitions and nomenclature

Several terms have been used to describe osteonecrosis of the jaw, including osteoradionecrosis (ORN), "phossy jaw,"

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avascular necrosis of the jaw, and bisphosphonate-related or -associated osteonecrosis of the jaw. ORN is distinctly different from BIONJ in that ORN patients experience hypoxic tissue changes in a localized area of radiation exposure.[8] In addition, ORN patients typically respond to treatment (e.g., hyperbaric oxygen, surgical debridement or resection and subsequent reconstruction of the necrotic segment), whereas BIONJ patients often do not.[9–11] Similarly, the term "phossy jaw" is more correctly used to describe nonhealing bone found only in the mouth of phosphate miners and match-factory workers in the late 1800s.[10]

Finally, the scientific literature includes such terms as avascular necrosis of the jaw, bisphosphonate-related osteonecrosis of the jaw, and bisphosphonate-associated osteonecrosis of the jaw.[1,3-5,11] The most recent evidence supports a more specific term: BIONJ. Patients are considered to have BIONJ if they fulfill the following 3 criteria:

1. *Current or previous treatment with a bisphosphonate*
2. *Exposed bone in the maxillofacial region that has persisted for more than 8 weeks*
3. *No history of radiation therapy to the jaws*[4]

History

The first description of exposed, nonhealing bone in the mouths of patients receiving intravenous (IV) bisphosphonate medication was in a 2002 textbook by Marx and Stern;[12] however, the relationship between bisphosphonate use and bone exposure was not fully appreciated at that time.

In September 2003, Marx[13] published a series of 36 cases of what was then termed "avascular necrosis" in patients being treated with IV bisphosphonates, zolendronic acid and pamidronate. In the following month, the medication's manufacturer, Novartis,[i] issued a denial of any causal relationship.[1] Then in December 2003, and March 2004, Marx and other colleagues[14] involved in the care of patients receiving bisphosphonates were invited by Novartis to participate in a review of cases in an attempt to further define the problem. The result was development of recommendations for treating BIONJ patients.[15]

In April 2004, Estillo and Van Posnak[16] published a retrospective case study report. This was followed in May by Ruggeirio's report[17] on a series of 63 patients with BIONJ. A precaution was added to the labels of zolendronic acid and pamidronate, and the medical community was informed via a "Dear Doctor" letter[18] regarding the potential for BIONJ. While the vast majority of patients were taking the IV forms of bisphosphonate drugs, a small number of patients were taking an oral form, alendronate or residronate and, in July of 2005, the United States Food and Drug Administration (FDA) required that a cautionary statement[19] be added to the alendronate product literature.

However, perhaps the most noteworthy article in terms of public notification of the problem appeared in the *Wall Street Journal* in December 2004.[20] As print and electronic media began to pick up the story, public awareness grew quickly, and the number of case reports increased.

One question, however, continues to mystify clinicians: Why wasn't BIONJ seen in the studies that preceded FDA approval of the bisphosphonate drugs? In fact, 6 cases of BIONJ were diagnosed during these studies,[21] but it was not recognized that the abnormality might be secondary to the bisphosphonate medication.

To date, more than 2,000 cases of BIONJ have been reported to the FDA,[22] but it is essential for clinicians to maintain perspective on the bisphosphonate problem. In an editorial in the *Journal of Oral and Maxillofacial Surgery*, Assael[22] stated, "While this is an important clinical problem, it should not be allowed to deny patients the important benefits of these drugs or prevent researchers from investigating the potential benefits yet to be gained from bisphosphonates ... Bisphosphonates have done enormous good in fending off hypercalcemia in malignancy, decreasing bone pain and decreasing the risk of often catastrophic pathologic fracture of the femoral neck or spine." Although some successful therapeutic protocols for treating BIONJ patients have been reported,[4,23] to date, no well-controlled prospective studies of treatment outcomes exist.

Bone metabolism

In order to understand the action of bisphosphonates, it is essential to first review normal bone metabolism. The skeleton, along with the coordinated efforts of the kidneys, parathyroid glands, and intestines, plays a significant role in maintaining calcium homeostasis in the body.[24] The skeleton consists of hard cortical bone and trabecular bone. Within trabecular bone is the bone marrow, which is filled with precursor cells capable of differentiating into osteoclasts or osteoblasts. These are the 2 predominant cells responsible for bone remodeling and they secrete substances that either act on other cells or become immobilized in the mineral matrix of bone.[25] Osteoblasts mature into osteocytes which are the most numerous cell type in the mineralized bone matrix. This mineralized matrix becomes a rich source of a number of growth factors, including insulin-like growth factors 1 and 2 (IGF_1 and IGF_2) and bone morphogenic protein (BMP).[26]

[i] East Hanover, NJ

As serum calcium decreases, the parathyroid gland is stimulated to produce parathyroid hormone (PTH). One of the biological actions of PTH is to stimulate osteoclastic bone resorption in an effort to release calcium from the bone into the bloodstream. PTH stimulates the release of the receptor activator of nuclear factor κB ligand (RANK-L) from the membrane of the osteoblast. RANK-L binds to the osteoclast receptor (RANK), causing osteoclastic stimulation and bone resorption. Osteoprotegerin (OPG) is a decoy receptor that competes with the RANK receptor for association with RANK-L. When RANK-L is bound to OPG it is not available to bind to the osteoclast, thereby reducing bone resorption.[24] Therefore, osteoclastic activation or inhibition is regulated by the RANK ligand system (Figure 1).

The stimulated osteoclast secretes acid into the mineral matrix, releasing IGF_1, IGF_2, and BMP. These then bind to the osteoblast precursors, resulting in differentiation, stimulation and maturation into osteoblasts which are responsible for bone formation. Figure 2 provides a slide of a histological section of viable bone.

In cancer patients, this precise hormonal and cellular regulation is significantly, and often lethally, disrupted. Systemically, multiple tumor factors are secreted, including PTH-related protein (PTHrP), resulting in exacerbated PTH-like function. In certain cancers (e.g., lung, breast, and prostate), bone metastases are common[24] most commonly involving the axial skeleton, particularly the long bones, pelvis, and vertebrae.[27] Osteolytic metastases locally produce PTHrP, which stimulates RANK-L production and inhibits OPG secretion from osteoblasts, thereby activating excessive osteoclastic resorption. The results of this osteolysis include hypercalcemia of malignancy, pathologic fractures, including vertebral compression fractures, and compression of neural foramina, including direct compression of the spinal cord.

Osteoporosis also represents an imbalance in bone remodeling, but to a much lesser extent. In healthy individuals, resorbed bone is replaced by an equal amount of new bone; in individuals with osteoporosis, resorption exceeds formation.[28] Increased osteoclastic activity and/or decreased osteoblastic activity are integral components of this imbalance. The various aspects of osteoporosis are discussed elsewhere in this issue of *Grand Rounds in Oral-Systemic Medicine*,[29] but it should be noted that osteoporosis can be a debilitating and sometimes lethal disease. Twenty percent of patients who sustain a hip fracture secondary to osteoporosis die in the ensuing 3 months; 50% never walk again.[30]

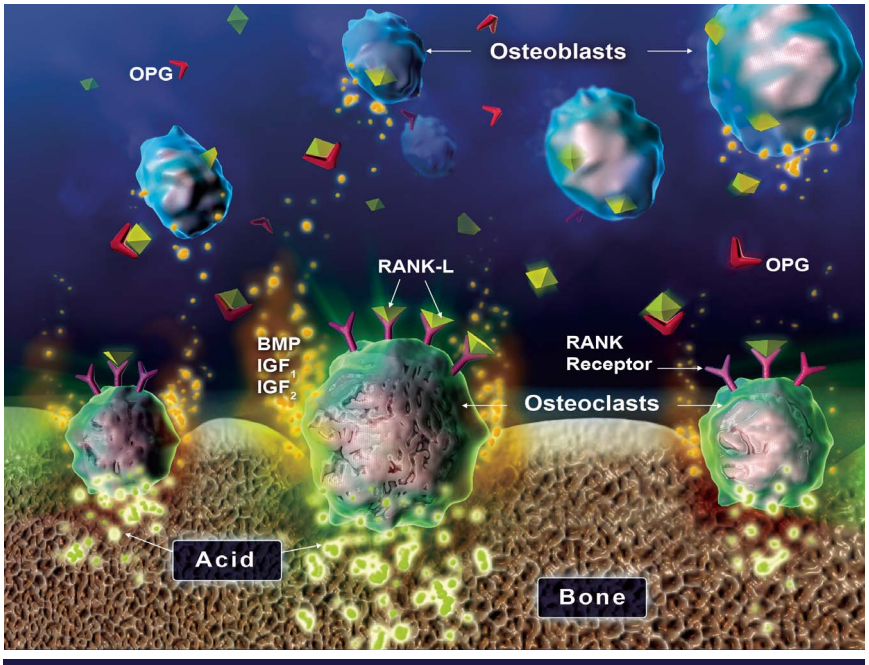

Figure 1: Cellular function in bone metabolism

At the cellular level, bone metabolism is largely mediated by the RANK ligand system. Osteoblasts secrete RANK-L which binds to the RANK receptor on the osteoclast causing bone resorption. As the osteoclast dissolves bone, IGF_1 and IGF_2, along with BMP, are released from the bone and cause osteoblastic growth, producing new bone. OPG competes with the RANK receptor to bind RANK-L, thereby inhibiting osteoclastic bone resorption.

Bisphosphonates

Bisphosphonates were first synthesized by chemists in the late 1950s as a viable substitute for polyphosphate, a compound used in detergent manufacturing that caused scale to form in manufacturing boilers. However, in 1964 the use of these compounds was discontinued by the Environmental Protection Agency because they were not biodegradable.[30]

In 1966 bisphosphonates were first administered to living animals, and an increase in bone mass was noted. In the late 1970s low bone mass was shown to be associated with fracture, and by 1984 the 2 concepts had been linked. Eleven years later, the oral bisphosphonate alendronate was approved by the FDA for the treatment of osteoporosis.[30] Relatively soon thereafter other oral agents, residronate and ibandronate, were approved. The first injectable form of bisphosphonate, pamidronate, was approved for the treatment of bone metastases in 1991, and the more potent zolendronic acid

received approval 10 years later.[17] A third injectable agent, ibandronate, was approved for use in osteoporosis patients in 2006.[31]

Bisphosphonates do not kill osteoblasts as might be assumed. Rather, they interrupt the cycle responsible for osteoclastic structure.[30] Specifically, the nitrogen-containing bisphosphonates inhibit the conversion of dimethylallyl diphosphate into farnesyl diphosphate, which is important for the structural integrity of osteoclasts.[30] Without prenylation of their guanosine triphosphate–binding proteins, the osteoclasts undergo apoptosis. Without osteoclastic function, the bone becomes devoid of its cellular components (Figure 3) and unable to remodel. In addition, bisphosphonates affect osteoblastic activity, resulting in increased production of OPG. OPG has a competitive inhibitory effect on RANK-L, thereby further decreasing osteoclastic stimulation.[32]

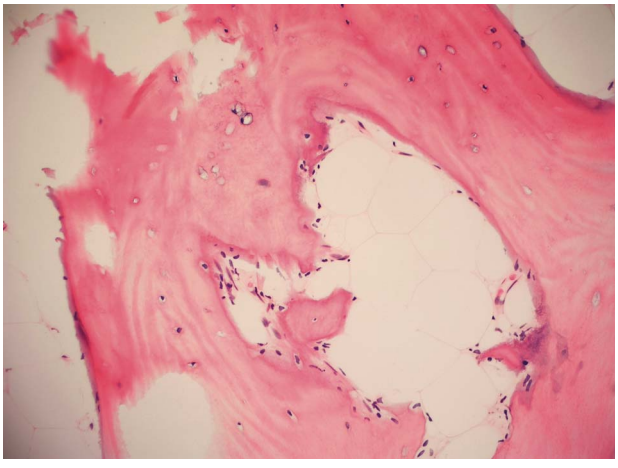

Figure 2: Histological section of viable bone

This slide demonstrates normal bone with osteocytes within the lacunae and the usual complement of osteoblasts and osteoclasts.

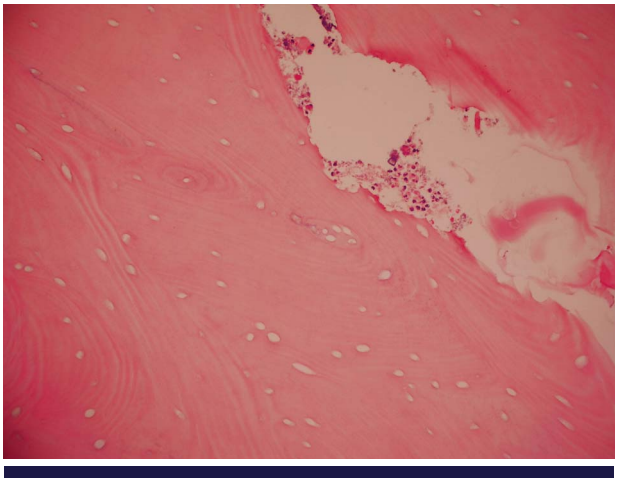

Figure 3: Histological section of necrotic bone tissue

In contrast to the previous slide of viable bone (Figure 2), in this image of bone, the lacunae are devoid of osteocyctes and there is no evidence of osteoclastic or osteoblastic activity. In addition, scattered collections of neutrophils and focal bacterial colonization are seen.

Five different nitrogen-containing bisphosphonate agents are currently available in the U.S.[30,33] (See Table 1 entitled *Bisphosphonate Agents Currently Available in the U.S.*, which may be accessed and downloaded from the *Clinical Decision-Making Tools* section at www.thesystemiclink.com). Two other bisphonsphonates, etidronate and tiludronate, are non-nitrogen-containing agents used primarily in the treatment of patients with Paget's disease and have not been implicated in BIONJ. Their potencies are approximately 1,000 times less than those of the weakest nitrogen-containing bisphosphonates.[33]

In a lecture to the American Association of Oral and Maxillofacial Surgeons, Kimmel[30] proposed the concept of an "anti-resorptive unit" (AR), a unit of measure that could be used to compare the potencies of bisphosphonates in terms of their anti-resorptive action. For example, the injectable bisphosphonates zolendronic acid and pamidronate have a potency of 80 to 100 AR/month, which is 30 to 40 times the potency of the oral bisphosphonates alendronate, residronate, and ibandronate (2 to 6 AR/month). This significant difference accounts for the earlier onset of BIONJ in patients treated with IV agents (6 to 12 months) compared with oral agents (>3 years). Both types of agents have extremely rapid uptake into the skeleton (50% within 30 minutes) and demonstrate a special affinity for areas of rapid bone turnover. Black and colleagues[34] postulated that because the alveolar processes demonstrate a 10-fold increase in bone turnover relative to other parts of the skeleton, this may be the reason that bisphosphonate-induced osteonecrosis to date has been found only in the jaw.

BIONJ incidence

The true incidence of BIONJ is difficult to determine for several reasons. First, because it is a relatively new entity, it has often gone unrecognized in patients treated for exposed bone in the oral cavity.

Second, the incidence of BIONJ is also difficult to determine because not all practitioners have reported known cases to MedWatch,[ii] thereby leading to under-reporting of the disease.

[ii] FDA Safety Information and Adverse Event Reporting Program. Available at: http://www.fda.gov/medwatch/

Third, online surveys of cancer patients that have been conducted are not controlled and may result in only a small population of interested patients answering the survey with a potential for over-reporting.

Perhaps the best estimate of BIONJ incidence in cancer patients comes from a retrospective chart review[35] of 297 multiple myeloma patients, 81 breast cancer patients, and 69 prostate cancer patients who received bisphosphonate therapy between January 1, 2000, and December 31, 2005. The results showed an incidence of 5.39% in multiple myeloma patients, 2.5% in breast cancer patients, and 2.9% in those with prostate cancer.

Determining the incidence of BIONJ in patients taking oral bisphosphonates is made even more difficult by the fact that the actual number of patients receiving these medications is not known and can only be estimated. One estimate, based on numbers of prescriptions written for alendronate, established an incidence of 0.007%, or 0.7/100,000 person-years of exposure.[36] In Australia the estimated incidence of BIONJ in patients treated with alendronate is 0.01% to 0.04%, again based on prescription data.[4] After tooth extraction this rate increased to 0.09% to 0.34%. Although these numbers appear quite small, they must be viewed in the light of Intercontinental Marketing Services Health[iii] data showing that to date, more than 190 million prescriptions for oral bisphosphonates have been dispensed worldwide.[37]

Diagnosis of BIONJ

Signs and symptoms. BIONJ patients may present with various complaints. Marx and Sawatari found that 68.9% of patients presented with an area of exposed bone and pain, 31.1% presented with asymptomatic exposed bone, 23.5% with 1 or more mobile teeth, and 17.6% with a cutaneous fistula, mucosal fistula, or bone exposed through the skin.[23] An expert panel[38] also noted that patients may have more subtle complaints, such as a feeling of heaviness in the jaw or numbness. Eighty-one (68.1%) bone exposures occurred in the mandible alone, 33 (27.7%) in the maxilla, and 5 (4.2%) occurred in both jaws.[23]

Imaging. In the early stages of BIONJ, plain radiography is not especially useful. The most common findings are a hyperostotic lamina dura and widened periodontal ligament.[23,39] However, periapical and panoramic radiographs are helpful in ruling out other causes of dental pain, as well as metastatic lesions.

In more advanced cases, the clinician may diagnose larger areas of osteolysis, sequestra, or osteomyelitis. Computerized axial tomography may assist in identifying the extent of these more severe sequelae and is essential if a resection is planned.

Laboratory examination. Recently, a serum test used to evaluate bone turnover has been successfully applied in BIONJ patients. The C-terminal cross-linked telopetide (CTx) test has been used in metabolic studies as an indicator of the rate of bone renewal.[40,41] Chailurkit stated, "Biochemical markers of bone turnover appear to be of use in assessing early response to therapy. Bone resorption markers, especially serum CTx, are better indicators than bone formation markers for estimating the response to therapy in early postmenopausal women."[42] Marx[39] has established that serum CTx values <100 pg/mL are associated with a high risk of developing BIONJ; values of 100 to 150 pg/mL, a moderate risk; and values >150 pg/mL, minimal to no risk.

The CTx test is performed by Quest Diagnostics[iv] at 1 of 2,000 service centers across the country. Locations may be identified online at http://www.questdiagnostics.com. The test must be ordered by a qualified health professional and the patient must fast for 12 hours beforehand. A small amount of blood is drawn and sent to the Quest Diagnostics facility in California, and results are available in 5-7 working days.[43]

Treatment of BIONJ

Before beginning IV bisphosphonate therapy, patients should be examined by a dentist and an oral and maxillofacial surgeon who are knowledgeable about BIONJ. Appropriate consultations from other dental specialists are advised, especially the input of the periodontist. Appropriate imaging studies should be performed and correlated with the clinical examination. If the patient has existing dental needs, the treating physician and the dentist must decide whether to delay therapy until dental health is achieved.[4] Any such patient must then become a priority for treatment by the dental team. If extractions or other dentoalveolar surgery are necessary, adequate time for bone healing must be allowed prior to initiating IV bisphosphonate treatment. The length of this healing period depends on the type of procedure being performed and on the patient's overall systemic health, but a period of 4 to 8 weeks is ideal. The goal of treatment for this group of patients is to support them in such a manner that they can continue with oncologic treatment.[4] This support would include addressing significant periodontal needs, completing any restorative treatment that might preclude a tooth from becoming abscessed, and adjusting any removable prosthesis to assure there will be no soft tissue breakdown after bisphosphonate treatment has begun. Consideration should be given to removal of large,

[iii] www.imshealth.com

[iv] Corporate Headquarters, Plymouth Meeting, PA

multilobular mandibular tori since they are often sites where BIONJ develops. It is imperative that these decisions be made with the patient's oncologist.[4,36] Guidelines for handling dental needs that arise in patients already receiving bisphosphonate therapy depends on proper staging of their BIONJ.

Staging of BIONJ

Determining the stage of BIONJ is necessary to direct medical therapy and establish the patient's prognosis. A staging system proposed by the American Association of Oral and Maxillofacial Surgeons[4] has been modified by the authors to include CTx testing and is discussed in the text that follows.

Stage 0. Stage 0 patients are typically asymptomatic and are receiving IV bisphosphonates (Stage 0_{IV}) or have been taking oral bisphosphonates for more than 3 years (Stage 0_{Or}). In patients receiving IV bisphosphonates, nonrestorable teeth may be treated by removal of the crown and endodontic treatment of the remaining root.[5] Oral implants or other dentoalveolar surgery should be avoided. Oral hygiene must be diligently maintained.

Stage 0 oral bisphosphonate patients should have treatment deferred, if possible, until a serum CTx level has been obtained. CTx levels >150 pg/mL indicate that dentoalveolar surgery is relatively safe.[33] For those patients with CTx levels <150 pg/mL, the prescribing physician should be contacted to see if the patient can be withdrawn from the bisphosphonate medication for a period of 3 months.[39] If the CTx level remains below 150 pg/mL, the drug holiday is extended for another 3 months. This is repeated until the level is above 150 pg/mL, at which time dental treatment may be rendered. If emergency treatment must be done, a CTx level should be obtained as soon as possible after the procedure and the physician is contacted. Appropriate informed consent must be obtained from the patient prior to initiating the procedure.

In 1 author's (MLW) experience with a small series of patients taking oral bisphosphonates (alendronate or residronate) for more than 3 years, initial CTx levels ranged from 33 to 280 pg/mL. In all cases where the CTx level was low, the treating physician was willing to have the patient suspend bisphosphonate treatment for several months.

Stage I. Stage I_{IV} and Stage I_{Or} patients present with asymptomatic exposed bone. Because the priority for patients receiving IV bisphosphonates is to continue bisphosphonate treatment, a detailed oral examination and noninvasive treatment plan should be undertaken by the dentist, oral and maxillofacial surgeon, and any other involved dental specialists, in close collaboration with the oncology team. The patient should be educated about the exposed bone, instructed in proper oral hygiene of the area, and placed on a maintenance regimen of chlorhexidine oral rinses and frequent follow-up visits.[4] The dentist should watch for any signs of soft or hard tissue infection or additional exposed bone.

Stage I_{Or} patients should initially follow the same regimen. However, a baseline CTx level should be obtained and the treating physician contacted to investigate the possibility of discontinuing bisphosphonate medication. Once again a comprehensive dental examination should be performed and treatment carefully planned. If possible, the patient's dental needs should be temporized or delayed until the CTx level rises above 150 pg/mL.

Stage II. Stage II patients present with exposed bone, pain, and soft tissue or bone infections.[38] Stage II_{IV} patients should have cultures taken to determine appropriate antibiotic therapy. Treatment should be directed toward the results of those cultures; however, not infrequently, oral culture results are read as "normal oral flora." In such cases, the clinician should consider empiric therapy. Appropriate antibiotic and fungal regimens[44] are shown in Tables 2 and 3, respectively. (Table 2 entitled *Antibiotic Regimens for Patients with BIONJ* may be accessed and downloaded from the *Clinical Decision-Making Tools* section at www.thesystemiclink.com. Table 3 entitled *Antifungal Regimens for Patients with BIONJ* may be accessed and downloaded from the *Clinical Decision-Making Tools* section at www.thesystemiclink.com.)

The standard regimen for Stage II_{IV} or Stage II_{Or} BIONJ is penicillin V potassium 500 mg every 6 hours and an oral rinse using chlorhexidine 0.12% twice daily.[20,23] In refractory cases, metronidozole 500 mg every 6 hours is added for 7 to 10 days.[4,23] For patients who are allergic to penicillin, monotherapy with clindamycin may not be sufficient; such therapy has not been efficacious in some cases,[20,23] possibly because of clindamycin's lack of activity against *Actinomyces* spp. and *Eikenella corrodens*.[20,23] Levofloxacin 500 mg daily has proved to be an excellent alternative.[45]

In Stage II_{Or} patients, the only difference in treatment is that the bisphosphonate medication is more likely to be discontinued for several months. A CTx level should be obtained as a baseline measurement, and more extensive treatment may proceed when the level exceeds 150 pg/mL.

Stage III. Stage III patients present with all of the preceding signs and symptoms and at least 1 of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border.[4] In these patients, more conservative treatment methods may have already failed. Therefore, to alleviate pain and eliminate infection, it may

be necessary to debride or resect large areas of bone;[4] this approach has met with some success.[17,20,23,38,45] Curi and colleagues[44] have described 3 cases in which adjunctive treatment was combined with surgery, but to date no standardized treatment protocols exist. The following case report illustrates 1 private practitioner's (MLW) experience in caring for a cancer patient who was receiving IV bisphosphonate therapy.

Case Report

RD is a 67-year-old white male who initially presented in January 2005 on referral from his dentist for "exposed bone on the lingual mandible" (Figure 4). The patient had completed endodontic treatment on tooth #30 six months previously, but the treatment did not relieve his pain. He complained of increasingly severe pain in the right mandible that radiated anteriorly and of swelling and purulent discharge. He had been diagnosed with renal cell carcinoma and had undergone removal of his right kidney. The cancer had metastasized to his right hip and he had undergone a right total hip replacement. He was being treated with high dose pain medication and zolendronic acid. The dental examination revealed a 2- to 3-mm-diameter area of exposed bone lingual to tooth #30, with anterior swelling, erythema, and 2 draining fistulae over a large multilobulated, lingual torus (Figures 4 and 5, [fistulae not visible on x-ray]). Treatment consisted of clindamycin 300 mg every 6 hours for 10 days, along with a hydrogen peroxide rinse 4 times daily.

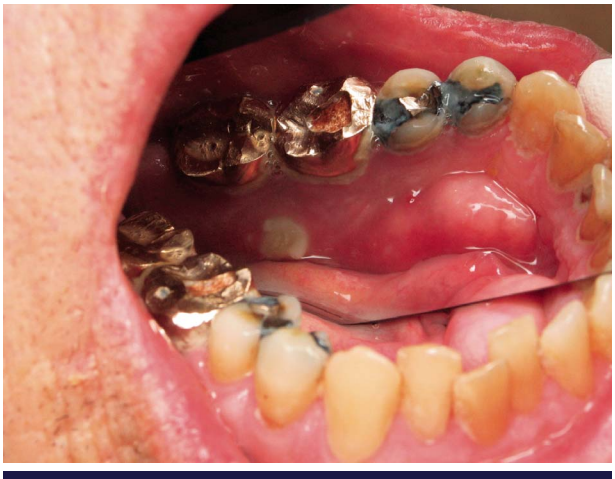

Figure 4

January 2005 *Initial presentation of patient taking zolendronic acid for metastatic renal cell carcinoma. Note small lingual mucosal dehiscence between teeth #30 and 31 and large, multilobulated torus (mirror view).*

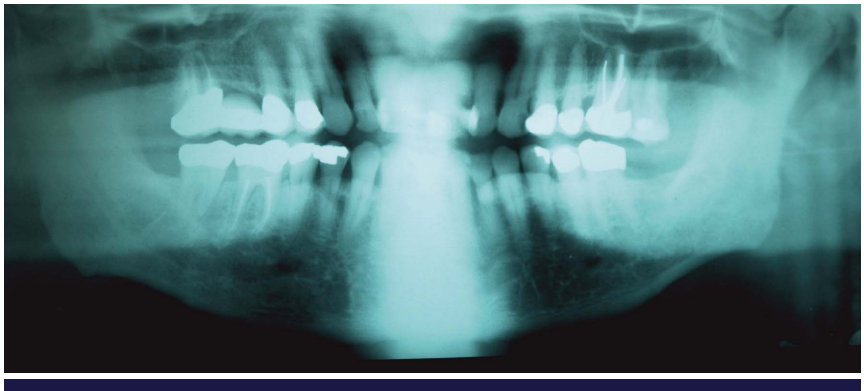

Figure 5

January 2005 *Initial radiograph demonstrating endodontic treatment of tooth #30, hyperostotic lamina dura and extremely dense lingual tori.*

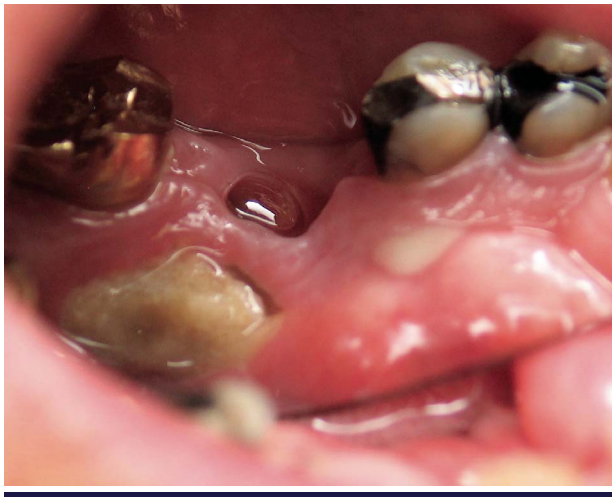

Figure 6

July 2005 *After extraction of #30, patient initially improved but returned with enlarged area of exposed bone and draining fistulae over torus.*

The patient's condition improved but did not resolve. The medication was changed to penicillin V potassium 500 mg every 6 hours, along with metronidazole 500 mg every 6 hours. The patient was then lost to follow-up for several months as a result of a change in health insurance.

In June 2005 the patient returned, complaining of pain, swelling, and discharge. After debridement of a small amount of sequestered bone, the patient was prescribed the same penicillin V potassium–metronidazole regimen as earlier. Because of

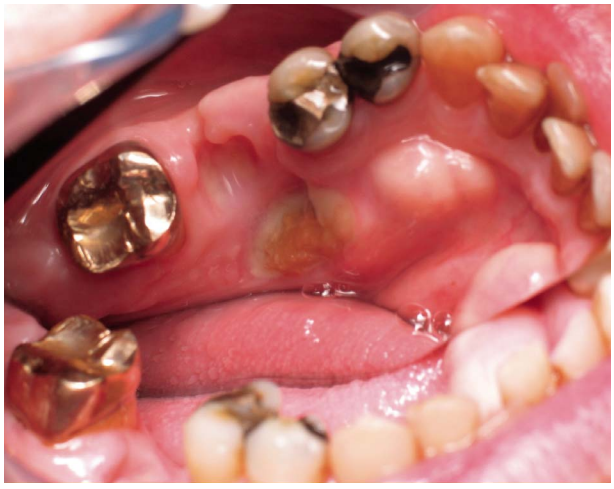

Figure 7

May 2006 *Exposed bone remains but patient is free of infection on maintenance antibiotics.*

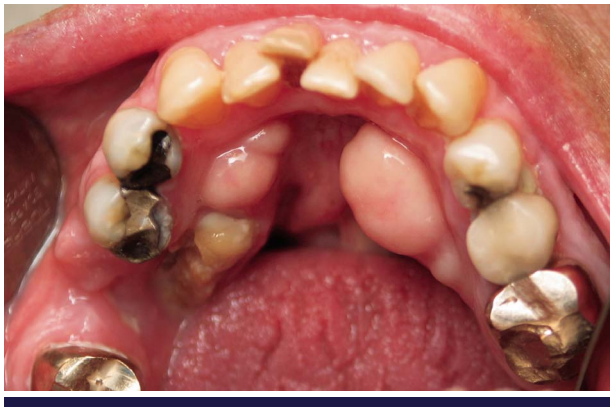

Figure 8

January 2007 *Exposed bone has enlarged with increased involvement of the torus 9 and supparation at the distal aspect of the exposure.*

continued pain and mobility, tooth #30 was extracted. During the procedure, an abscess was noted and infected tissue was debrided; treatment with penicillin and metronidazole was continued and the patient's pain resolved. He continued to struggle with poor oral hygiene on the necrotic segment.

In July 2005, a larger area of exposed bone was found lingual to tooth #30 (Figure 6). One month later, the necrotic bone was surgically debrided, and the antibiotic regimen was continued.

In March 2006, tooth #9 also developed an abcess. To avoid extraction of the tooth and the possibility of additional necrotic bone, the crown of tooth #9 was amputated, endodontic treatment was completed and the root was left in the bone. A small sequestrectomy was completed on the buccal bone of tooth #30 and antibiotic maintenance was continued with Pen VK 500 mg every 6 hours. Figure 7 demonstrates the patient's return to a non-infected status.

In January 2007 the patient presented once more with increasingly severe pain in the right mandible, with swelling and pus (Figure 8). The patient was treated with the PenVK/Metronidazole regimen and the infection resolved. He died of renal cell carcinoma in March 2007. This litany of care is illustrative of the challenges facing clinicians who care for bisphosphonate patients.

Conclusion

Bisphosphonate medications, which are used primarily to treat cancer patients and those with osteoporosis, have been linked to osteonecrosis of the jaw. While the majority of patients who develop BIONJ are cancer patients being given the IV form of the drug, the potential for BIONJ to develop in those taking these medications orally must be considered in patients presenting for dental care. As our understanding of this very complex issue continues to evolve, both dental and medical professionals must stay up to date on the literature and maintain open lines of communication in order to render the best care for their patients.

Acknowledgments

The authors would like to acknowledge Dr. Nancy Van Buren, Ms. Kathy Runge, and Ms. Teresa Wade for their assistance with this article.

References

1. Tarassoff P, Cermak K. Avascular necrosis of the jaws: risk factors in metastatic cancer patients. *J Oral Maxillofac Surg.* 2003;61:1238-1239.
2. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants.* 2006;21:349-353.
3. Migliorati CA, Casiglia J, Epstein J, et al. Managing the care of patients with bisphosphonate-associated osteonecrosis. An American Academy of Oral Medicine position paper. *J Am Dent Assoc.* 2005;136:1658-1668.
4. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. 2006; Sept 25. Available at: http://www.aaoms.org/docs/position_papers/osteonecrosis.pdf. Accessed Feb 1, 2007.

For additional references to this article, please consult the digital version of *Grand Rounds in Oral-Systemic Medicine*™ at www.thesystemiclink.com.

5. American Association of Endodontists Special Committee on Bisphosphonates, Endodontic Implications of Bisphosphonate-Associated Osteonecrosis of the Jaws. 2006. Available at: http://www.aae.org/dentalpro/guidelines.htm. Accessed Feb 1, 2007.
6. Marx RE. Oral and Intravenous Bisphosphonate-induced Osteonecrosis of the Jaws. 1st ed. Hanover Park, IL: *Quintessence*; 2007:64-66.
7. Zimmerman Reid Attorneys at Law. Fosamax and Bisphosphonate Side Effect and Litigation advertising material. 2007; Jan 26.
8. Marx RE. Osteoradionecrosis-a new concept of its pathophysiology. *J Oral Maxillofac Surg.* 1983;41:351.
9. Peleg M, Lopez EA. The treatment of osteoradionecrosis of the mandible: the case for hyperbaric oxygen and bone graft reconstruction. *J Oral Maxillofac Surg.* 2006;64:956-960.
10. Hellstein JW, Marek CL. Bisphosphonate chemonecrosis (bisphossy jaw): is this the phossy jaw of the 21st century? *J Oral Maxillofac Surg.* 2005;63:682-689.
11. Rosenberg TJ, Ruggerio S. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg.* 2003;62:527-534.
12. Marx RE, Stern DS. Oral and Maxillofacial Pathology: A Rational for Diagnosis and Treatment. 1st ed. Chicago, IL: *Quintessence*; 2002:36-38.
13. Marx RE. Pamidronate (Aredia) and zolendronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic? *J Oral Maxillofac Surg.* 2003;61:1155-1157.
14. Osteonecrosis of the jaw (ONJ) and bisphosphonates. Oncologic Drugs Advisory Committee. Mar 4, 2005. PowerPoint Presentation 2005-4095S2_04_01-Novartis-Zometa.ppt. Available at: http://www.fda.gov/ohrms/dockets/AC/05/slides/2005-4095S2_04_01-Novartis-Zometa.ppt. Accessed Mar 29, 2007.
15. Novartis Pharmaceuticals. Expert panel recommendations for the prevention, diagnosis and treatment of osteonecrosis of the jaw. Paper presented at: Oncology Advisory Committee Meeting; Mar 4, 2005.
16. Estilo CL, Van Poznak CH, Williams E, et. al. Osteonecrosis of the maxilla and mandible in patients treated with bisphosphonates: a retrospective study. *J Clin Oncol.* 2004 ASCO Meeting Proceedings (Post-Meeting Edition). 2004;22:8088.
17. Ruggerio SL, Mehrota B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates; a review of 63 cases. *J Oral Maxillofac Surg.* 2004;May;62:527-534.
18. Hohnecker JA. Novartis "Dear Doctor" Precautions added to label of Aredia and Zometa. Sept 24, 2004.
19. Fosamax (alendronate sodium) prescribing information. Merck and Co., Inc. Whitehouse Station NJ 08889. Nov 2006, p 13.
20. Anand G. Jaw ailment shows industry moves slowly. *Wall Street Journal.* 2004;Dec 8. Available at: http://www.wsj.com. Accessed Feb 13, 2007.
21. FDA Oncologic Drugs Advisory Committee Volume II. Transcript Mar 4, 2005. Available at: http://www.fda.gov/ohr ms/dockets/ac/05/transcripts/2005-4095T2.htm. Accessed Mar 29, 2007.
22. Assael LA. A time for perspective on bisphosphonate. *J Oral Maxillofac Surg.* 2006;64:877-879.
23. Marx RE, Sawatari Y, Fortin M, et al. Bisphosphonate induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg.* 2005;63:1567-1575.
24. Clines GA, Guise TA. Hypercalcemia of malignancy and basic research on mechanisms responsible for osteolytic and osteoblastic metastasis to bone. *Endocr-Relat Cancer.* 2005;12:549-583.
25. Yoneda T. Mechanisms of preferential metastasis of breast cancer to bone. *Int J Oncol.* 1996;9:103-109.
26. Hauschka PV, Mavrakos AE, Iafrati MD, et al. Growth factors in bone matrix. Isolation of multiple types by affinity chromatography on heparin-sepharose. *J Biol Chem.* 1986;261:12665-12674.
27. Galasko CSB. Relationship of bone destruction in skeletal metastases to osteoclast activation and prostaglandins. *Nature.* 1976;263:508-510.
28. Lindsay R, Cosman F. Osteoporosis: Harrison's internal medicine online. Available at: http://www.accessmedicine.com. Accessed Feb 6, 2007.
29. Oh T, Bashutski J, Giannobile W. The interrelationship between osteoporosis and oral bone loss. *Grand Rounds Oral-Sys Med.* 2007;2:10-21.
30. Kimmel D. Symposium on Bisphosphonate Induced Bone Necrosis. *AAOMS 87th Annual Meeting Session 98 SM-10.* 2005; Sept 21-28.
31. Waknine,Y. FDA Approvals: Boniva and Femara, *Medscape Today*. Jan 12, 2006. Available at www.medscape.com/viewarticle/521326. Accessed Apr 24, 2007.
32. Viereck V, Emons G, Lauck V, et al. Bisphosphonates pamidronate and zoledronic acid stimulate osteoprotegerin production by primary human osteoblasts. *Biochem Biophys Res Commun.* 2002;291:680-686.
33. Marx RE. Oral and Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws. 1st ed. Hanover Park, IL. *Quintessence*; 2007:9-12
34. Black DS, Thompson DE, et. al. Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. *J Clin Endocrinol Metab.* 2000;85:4118-4124.
35. Wang EP. Risk of osteonecrosis of the jaw in multiple myeloma, breast and prostate cancer patients on high dose bisphosphonate therapy. *J Oral Maxillofac Surg.* 2006;64:30-31.
36. Report of the Council of Scientific Affairs. Expert Panel Recommendations: Dental Management of Patients on Oral Bisphosphonate Therapy. American Dental Association. June 1996. Available at: http://www.ada.org/prof/resources/topics/osteonecrosis.asp. Accessed June 29, 2006.
37. IMS Health, NPA Plus. May 2006 as cited in AAOMS Position Paper on Bisphosphonates-Related Osteonecrosis of the Jaws. Available at: http://www.aaoms.org/docs/position_papers/osteonecrosis.pdf. Accessed Feb 2, 2007.

38. Ruggiero S, Gralow J, Mark RE, et al. Practical guidelines for the prevention, diagnosis and treatment of osteonecrosis of the jaw in patients with cancer. *J Oncol Pract.* 2006;2:7-14.
39. Marx RE. Oral and Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws. 1st ed. Hanover Park, IL. *Quintessence*; 2007:83-93.
40. Rosen HN, Parker RA, Greenspan RL, et al. Evaluation of ability of biochemical markers of bone turnover to predict a response to increased doses to HRT. *Calcif Tissue Int.* 2004;74:415-423.
41. Guillemont J, Acarie C, Penes G, et al. Acute effects of an oral calcium load on markers of bone metabolism during endurance cycling exercise in male athletes. *Calcif Tissue Int.* 2004;74:407-414.
42. Chailurkit L, Ongphiphadhanakul B, Piaseu N, et al. Biochemical markers of bone turnover and response of bone mineral density to intervention in early postmenopausal women: an experience in a clinical laboratory. *Clin Chem.* 2001;47:1083-1088.
43. Cofield M. Medical Director, Quest Diagnostics, personal communication, Feb 2007.
44. Cossolin GS, dos Santos MO, Curi MM, et al. Treatment of avascular osteonecrosis of the mandible in cancer patients with a history of bisphosphonate therapy by combining bone resection and autologous platelet rich plasma: report of three cases. Available at: http://www.premiooncoamericalatina.com/trabalhos/TRABALHOS%20CIENT%CDFICOS/009cielai.pdfl. Accessed Mar 13, 2007.
45. Durie B. Aredia/Zometa and osteonecrosis of the jaws, a new update. July 2004. Available at: http://www.myeloma.org/main.jsp?type=article&tab_id=1&menu_id=0&id=1259. Accessed Mar 28, 2007.

As a courtesy to the professions, *Grand Rounds in Oral-Systemic Medicine*™ has provided patient education materials and templates of letters to assist dentists in developing collaborative relationships with the medical community. Readers are invited to reproduce these copyrighted materials by accessing and downloading (for free) this information from **www.thesystemiclink.com**.

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Editor's Note: Our best and brightest dental and dental hygiene students have an opportunity to actively participate in the design and development of important patient education materials. This not only enhances students' educational experiences but it also provides them with useful publication skills so that they can become the next generation of journal contributors and effective advocates for the clinically applied mission of *Grand Rounds*. The honor of being selected as the student author of patient education materials is offered to students at all dental and dental hygiene schools. We encourage faculties who work with promising students to submit their names for consideration for this honorary invitation to contribute to the editorial mission of *Grand Rounds*.

In this issue of *Grand Rounds*, we are happy to recognize Thomas A. Statz, a periodontal resident at the University of Iowa College of Dentistry (with oversight from faculty mentors Dr. Janet M. Guthmiller and Dr. Georgia K. Johnson) for his excellent work in preparing the patient education tool for implementation entitled "Osteoporosis and Oral Health: Potential for Thinning Jaw Bones". Thank you, Thomas. — CH

IMPLEMENTATION

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To assist dentists in developing collaborative relationships with the medical community, *Grand Rounds in Oral-Systemic Medicine*™ has provided templates for dentists working in collaboration with physicians of at-risk patients.

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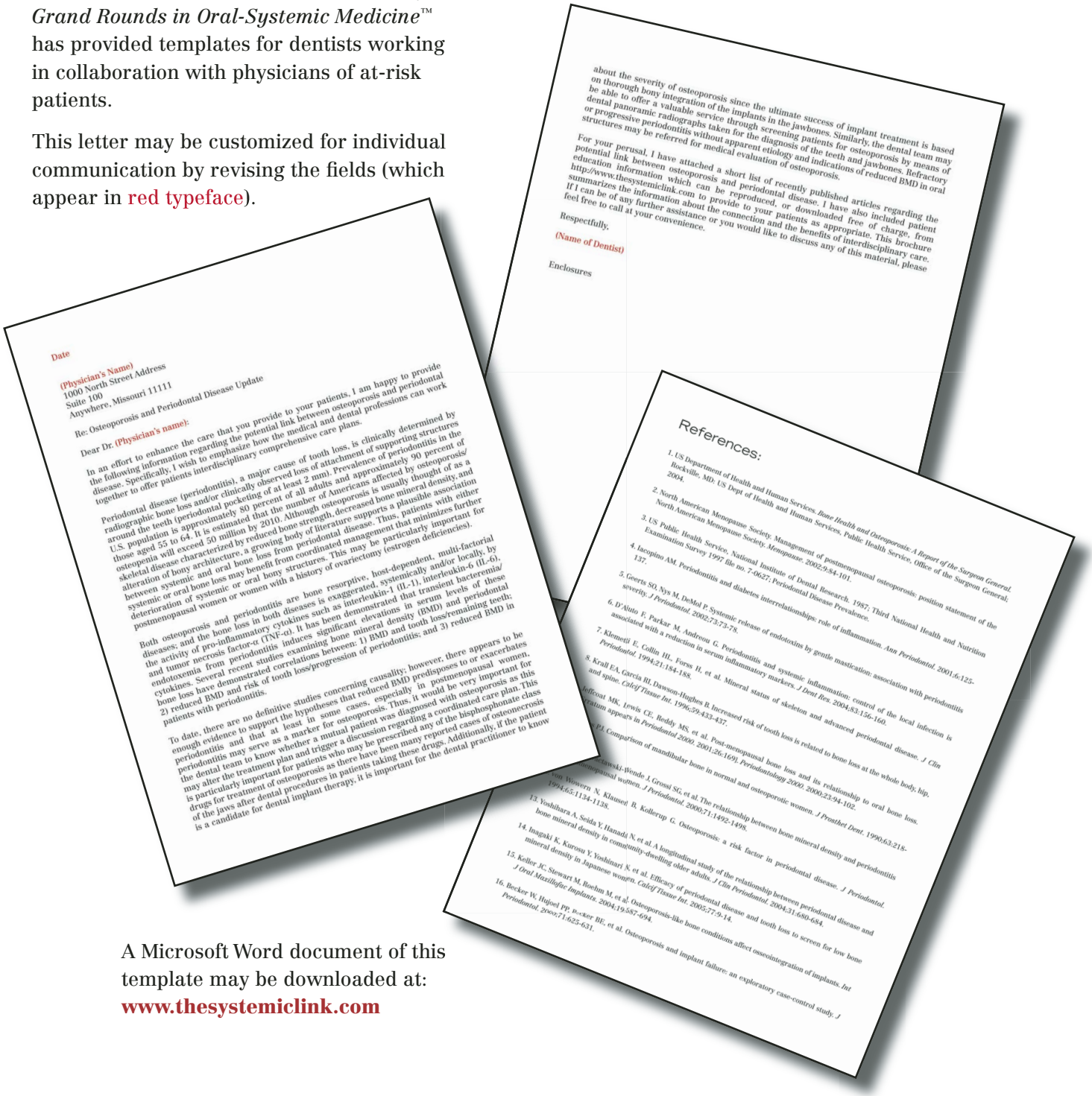

Date

(Physician's Name)
1000 North Street Address
Suite 100
Anywhere, Missouri 11111

Re: Osteoporosis and Periodontal Disease Update

Dear Dr. (Physician's name):

In an effort to enhance the care that you provide to your patients, I am happy to provide the following information regarding the potential link between osteoporosis and periodontal disease. Specifically, I wish to emphasize how the medical and dental professions can work together to offer patients interdisciplinary comprehensive care plans.

Periodontal disease (periodontitis), a major cause of tooth loss, is clinically determined by radiographic bone loss and/or clinically observed loss of attachment of supporting structures around the teeth (periodontal pocketing of at least 2 mm). Prevalence of periodontitis in the U.S. population is approximately 80 percent of all adults and approximately 90 percent of those aged 55 to 64. It is estimated that the number of Americans affected by osteoporosis/osteopenia will exceed 50 million by 2010. Although osteoporosis is usually thought of as a skeletal disease characterized by reduced bone strength, decreased bone mineral density, and alteration of bony architecture, a growing body of literature supports a plausible association between systemic and oral bone loss from periodontal disease. Thus, patients with either systemic or oral bone loss may benefit from coordinated management that minimizes further deterioration of systemic or oral bony structures. This may be particularly important for postmenopausal women or women with a history of ovariectomy (estrogen deficiencies).

Both osteoporosis and periodontitis are bone resorptive, host-dependent, multi-factorial diseases; and the bone loss in both diseases is exaggerated, systemically and/or locally, by the activity of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). It has been demonstrated that transient bacteremia/endotoxemia from periodontitis induces significant elevations in serum levels of these cytokines. Several recent studies examining bone mineral density (BMD) and periodontal bone loss have demonstrated correlations between: 1) BMD and tooth loss/remaining teeth; 2) reduced BMD and risk of tooth loss/progression of periodontitis; and 3) reduced BMD in patients with periodontitis.

To date, there are no definitive studies concerning causality; however, there appears to be enough evidence to support the hypotheses that reduced BMD predisposes to or exacerbates periodontitis and that at least in some cases, especially in postmenopausal women, periodontitis may serve as a marker for osteoporosis. Thus, it would be very important for the dental team to know whether a mutual patient was diagnosed with osteoporosis as this may alter the treatment plan and trigger a discussion regarding a coordinated care plan. This is particularly important for patients who may be prescribed any of the bisphosphonate class drugs for treatment of osteoporosis as there have been many reported cases of osteonecrosis of the jaws after dental procedures in patients taking these drugs. Additionally, if the patient is a candidate for dental implant therapy, it is important for the dental practitioner to know

about the severity of osteoporosis since the ultimate success of implant treatment is based on thorough bony integration of the implants in the jawbones. Similarly, the dental team may be able to offer a valuable service through screening patients for osteoporosis by means of dental panoramic radiographs taken for the diagnosis of the teeth and jawbones. Refractory or progressive periodontitis without apparent etiology and indications of reduced BMD in oral structures may be referred for medical evaluation of osteoporosis.

For your perusal, I have attached a short list of recently published articles regarding the potential link between osteoporosis and periodontal disease. I have also included patient education information which can be reproduced, or downloaded free of charge, from http://www.thesystemiclink.com to provide to your patients as appropriate. This brochure summarizes the information about the connection and the benefits of interdisciplinary care. If I can be of any further assistance or you would like to discuss any of this material, please feel free to call at your convenience.

Respectfully,

(Name of Dentist)

Enclosures

References:

1. US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General.* Rockville, MD: US Dept of Health and Human Services, Public Health Service, Office of the Surgeon General; 2004.
2. North American Menopause Society. Management of postmenopausal osteoporosis: position statement of the North American Menopause Society. *Menopause.* 2002;9:84-101.
3. US Public Health Service, National Institute of Dental Research. 1987; Third National Health and Nutrition Examination Survey 1997 file no. 7-0627; Periodontal Disease Prevalence.
4. Iacopino AM. Periodontitis and diabetes interrelationships: role of inflammation. *Ann Periodontol.* 2001;6:125-137.
5. Geerts SO, Nys M, DeMol P. Systemic release of endotoxins by gentle mastication: association with periodontitis severity. *J Periodontol.* 2002;73:73-78.
6. D'Aiuto F, Parkar M, Andreou G. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res.* 2004;83:156-160.
7. Klemetti E, Collin HL, Forss H, et al. Mineral status of skeleton and advanced periodontal disease. *J Clin Periodontol.* 1994;21:184-188.
8. Krall EA, García RI, Dawson-Hughes B. Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. *Calcif Tissue Int.* 1996;59:433-437.
9. Jeffcoat MK, Lewis CE, Reddy MS, et al. Post-menopausal bone loss and its relationship to oral bone loss. *Periodontol 2000.* 2001;26:169]. *Periodontology 2000.* 2000;23:34-102.
10. [illegible] PJ. Comparison of mandibular bone in normal and osteoporotic women. *J Prosthet Dent.* 1990;63:218-[illegible]
11. [illegible]awski-Wende J, Grossi SG, et al. The relationship between bone mineral density and periodontitis [illegible] women. *J Periodontol.* 2000;71:1492-1498.
12. [illegible] Wowern N, Klausen B, Kollerup G. Osteoporosis: a risk factor in periodontal disease. *J Periodontol.* 1994;65:1134-1138.
13. Yoshihara A, Seida Y, Hanada N, et al. A longitudinal study of the relationship between periodontal disease and bone mineral density in community-dwelling older adults. *J Clin Periodontol.* 2004;31:680-684.
14. Inagaki K, Kurosu Y, Yoshinari N, et al. Efficacy of periodontal disease and tooth loss to screen for low bone mineral density in Japanese women. *Calcif Tissue Int.* 2005;77:9-14.
15. Keller JC, Stewart M, Roehm M, et al. Osteoporosis-like bone conditions affect osseointegration of implants. *Int J Oral Maxillofac Implants.* 2004;19:587-694.
16. Becker W, Hujoel PP, [illegible]cker BE, et al. Osteoporosis and implant failure: an exploratory case-control study. *J Periodontol.* 2000;71:625-631.

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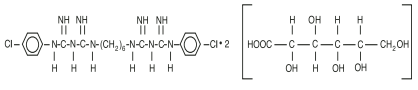
PERIDEX® ORAL RINSE
(CHLORHEXIDINE GLUCONATE 0.12%)

INDICATION: Peridex Oral Rinse is indicated for use between dental visits as part of a professional program for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding upon probing. Peridex Oral Rinse has not been tested among patients with acute necrotizing ulcerative gingivitis (ANUG). For patients having coexisting gingivitis and periodontitis, see PRECAUTIONS.

DESCRIPTION: Peridex is an oral rinse containing 0.12% chlorhexidine gluconate (1,1'-hexamethylene bis[5-(p-chlorophenyl) biguanide] di-D-gluconate) in a base containing water, 11.6% alcohol, glycerin, PEG-40 sorbitan diisostearate, flavor, sodium saccharin, and FD&C Blue No.1. Peridex is a near-neutral solution (pH range 5-7). Peridex is a salt of chlorhexidine and gluconic acid. Its chemical structure is:



CLINICAL PHARMACOLOGY: Peridex Oral Rinse provides antimicrobial activity during oral rinsing. The clinical significance of Peridex Oral Rinse's antimicrobial activities is not clear. Microbiological sampling of plaque has shown a general reduction of counts of certain assayed bacteria, both aerobic and anaerobic, ranging from 54-97% through six months use. Use of Peridex Oral Rinse in a six month clinical study did not result in any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem. Three months after Peridex Oral Rinse use was discontinued, the number of bacteria in plaque had returned to baseline levels and resistance of plaque bacteria to chlorhexidine gluconate was equal to that at baseline.

PHARMACOKINETICS: Pharmacokinetic studies with Peridex Oral Rinse indicate approximately 30% of the active ingredient, chlorhexidine gluconate, is retained in the oral cavity following rinsing. This retained drug is slowly released in the oral fluids. Studies conducted on human subjects and animals demonstrate chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. The mean plasma level of chlorhexidine gluconate reached a peak of 0.206 μg/g in humans 30 minutes after they ingested a 300mg dose of the drug. Detectable levels of chlorhexidine gluconate were not present in the plasma of these subjects 12 hours after the compound was administered. Excretion of chlorhexidine gluconate occurred primarily through the feces (~90%). Less than 1% of the chlorhexidine gluconate ingested by these subjects was excreted in the urine.

CONTRAINDICATIONS: Peridex Oral Rinse should not be used by persons who are known to be hypersensitive to chlorhexidine gluconate or other formula ingredients.

WARNINGS: The effect of Peridex Oral Rinse on periodontitis has not been determined. An increase in supragingival calculus was noted in clinical testing in Peridex Oral Rinse users compared with control users. It is not known if Peridex Oral Rinse use results in an increase in subgingival calculus. Calculus deposits should be removed by a dental prophylaxis at intervals not greater than six months. Hypersensitivity and generalized allergic reactions have occurred. SEE CONTRAINDICATIONS.

PRECAUTIONS:
GENERAL:

1. For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with Peridex Oral Rinse should not be used as a major indicator of underlying periodontitis.
2. Peridex Oral Rinse can cause staining of oral surfaces, such as tooth surfaces, restorations, and the dorsum of the tongue. Not all patients will experience a visually significant increase in toothstaining. In clinical testing, 56% of Peridex Oral Rinse users exhibited a measurable increase in facial anterior stain, compared to 35% of control users after six months; 15% of Peridex Oral Rinse users developed what was judged to be heavy stain, compared to 1% of control users after six months. Stain will be more pronounced in patients who have heavier accumulations of unremoved plaque. Stain resulting from use of Peridex Oral Rinse does not adversely affect health of the gingivae or other oral tissues. Stain can be removed from most tooth surfaces by conventional professional prophylactic techniques. Additional time may be required to complete the prophylaxis. Discretion should be used when prescribing to patients with anterior facial restorations with rough surfaces or margins. If natural stain cannot be removed from these surfaces by a dental prophylaxis, patients should be excluded from Peridex Oral Rinse treatment if permanent discoloration is unacceptable. Stain in these areas may be difficult to remove by dental prophylaxis and on rare occasions may necessitate replacement of these restorations.
3. Some patients may experience an alteration in taste perception while undergoing treatment with Peridex Oral Rinse. Rare instances of permanent taste alteration following Peridex Oral Rinse use have been reported via post-marketing product surveillance.

PREGNANCY: TERATOGENIC EFFECTS: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at chlorhexidine gluconate doses up to 300mg/kg/day and 40mg/kg/day respectively, and have not revealed evidence of harm to fetus. However, adequate and well-controlled studies in pregnant women have not been done. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Peridex Oral Rinse is administered to nursing women. In parturition and lactation studies with rats, no evidence of impaired parturition or of toxic effects to suckling pups was observed when chlorhexidine gluconate was administered to dams at doses that were over 100 times greater than that which would result from a person's ingesting 30ml of Peridex Oral Rinse per day.

PEDIATRIC USE:
Clinical effectiveness and safety of Peridex Oral Rinse have not been established in children under the age of 18.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY: In a drinking water study in rats, carcinogenic effects were not observed at doses up to 38mg/kg/day. Mutagenic effects were not observed in two mammalian in vivo mutagenesis studies with chlorhexidine gluconate. The highest doses of chlorhexidine used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1000mg/kg/day and 250mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100mg/kg/day.

ADVERSE REACTIONS: The most common side effects associated with chlorhexidine gluconate oral rinses are: 1) an increase in staining of teeth and other oral surfaces; 2) an increase in calculus formation; and 3) an alteration in taste perception; see WARNINGS and PRECAUTIONS. Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinse. The following oral mucosal side effects were reported during placebo-controlled adult clinical trials: aphthous ulcer, grossly obvious gingivitis, trauma, ulceration, erythema, desquamation, coated tongue, keratinization, geographic tongue, mucocele, and short frenum. Each occurred at a frequency of less than 1.0%.

Among post marketing reports, the most frequently reported oral mucosal symptoms associated with Peridex Oral Rinse are stomatitis, gingivitis, glossitis, ulcer, dry mouth, hypesthesia, glossal edema, and paresthesia.

Minor irritation and superficial desquamation of the oral mucosa have been noted in patients using Peridex Oral Rinse.

There have been cases of parotid gland swelling and inflammation of the salivary glands (sialadenitis) reported in patients using Peridex Oral Rinse.

OVERDOSAGE: Ingestion of 1 or 2 ounces of Peridex Oral Rinse by a small child (~10kg body weight) might result in gastric distress, including nausea, or signs of alcohol intoxication. Medical attention should be sought if more than 4 ounces of Peridex Oral Rinse is ingested by a small child or if signs of alcohol intoxication develop.

DOSAGE AND ADMINISTRATION: Peridex Oral Rinse therapy should be initiated directly following a dental prophylaxis. Patients using Peridex Oral Rinse should be reevaluated and given a thorough prophylaxis at intervals no longer than six months.

Recommended use is twice daily rinsing for 30 seconds, morning and evening after tooth brushing. Usual dosage is 15ml of undiluted Peridex Oral Rinse. Patients should be instructed to not rinse with water, or other mouthwashes, brush teeth, or eat immediately after using Peridex Oral Rinse. Peridex Oral Rinse is not intended for ingestion and should be expectorated after rinsing.

HOW SUPPLIED:
Peridex Oral Rinse is supplied as a blue liquid in:
- 16 fl. oz. (473ml) (NDC 51284-620-22)
  amber plastic bottles with child resistant dispensing closures
- 4 fl. oz. (118ml) (NDC 51284-620-12)
  amber plastic bottles with child resistant dispensing closures
- 64 oz. (NDC 51284-620-32)
  white plastic bottle with pump dispensing closure

DIRECTIONS FOR USE: Swish 15ml (one tablespoon) undiluted for 30 seconds, then spit out. Use after breakfast and before bedtime. Or, use as prescribed. NOTE: To minimize medicinal taste, do not rinse with water immediately after use.

WHAT TO EXPECT WHEN USING PERIDEX ORAL RINSE:
Peridex Oral Rinse is prescribed to treat gingivitis, to help reduce the redness and swelling of the gums, and also to help control any gum bleeding. Peridex Oral Rinse should be used regularly as directed by a dentist, in addition to daily brushing. Peridex should be spit out after use. It should not be swallowed.

Peridex Oral Rinse may cause some tooth discoloration, or increase in tartar (calculus) formation, particularly in areas where stain and tartar usually form. It is important to see a dentist for removal of any stain or tartar at least every six months or more frequently if a dentist advises.

- Both stain and tartar can be removed by your dentist or hygienist. Peridex Oral Rinse may cause permanent discoloration of some front-tooth fillings.
- To minimize discoloration, you should brush and floss daily, emphasizing areas which begin to discolor.
- Local hypersensitivity and sometimes generalized allergic reactions have also been reported. Peridex Oral Rinse should not be used by persons who have a sensitivity to it or its components.
- Peridex Oral Rinse may taste bitter to some patients and can affect how foods and beverages taste. This will become less noticeable in most cases with continued use of Peridex Oral Rinse.
- To avoid taste interference, rinse with Peridex Oral Rinse after meals. Do not rinse with water or other mouthwashes immediately after rinsing with Peridex Oral Rinse.

If you have any questions or comments about Peridex Oral Rinse, contact your dentist or pharmacist.

STORE ABOVE FREEZING (32°F or 0°C)
Caution: Federal law prohibits dispensing without prescription.

REFERENCES: 1. Data on file. OMNII Oral Pharmaceuticals. 2. Briner WW, Kayrouz GA, Chanak MX. Comparative antimicrobial effectiveness of a substantive (0.12% chlorhexidine) and a nonsubstantive (phenolic) mouthrinse in vivo and in vitro. *Compendium*. 1994 Sep;15(9):1158, 1160, 1162 passim; quiz 1170. 3. Balbuena L. Stambaugh KI, Ramirez SG, Yeager C. Effects of topical oral antiseptic rinses on bacterial counts of saliva in healthy human subjects. *Otolaryngol Head Neck Surg*. 1998 May; 118(5):625-9. 4. Gultz J, Kaim JM, DeLeo J 4th, Scherer W. An in vivo comparison of the antimicrobial activities of three mouthrinses. *J Clin Dent*. 1998;9(2):43-5. 5. Logothetis DD, Martinez-Welles JM. Reducing bacterial aerosol contamination with a chlorhexidine gluconate pre-rinse. *J Am Dent Assoc*. 1995 Dec;126(12):1634-9.

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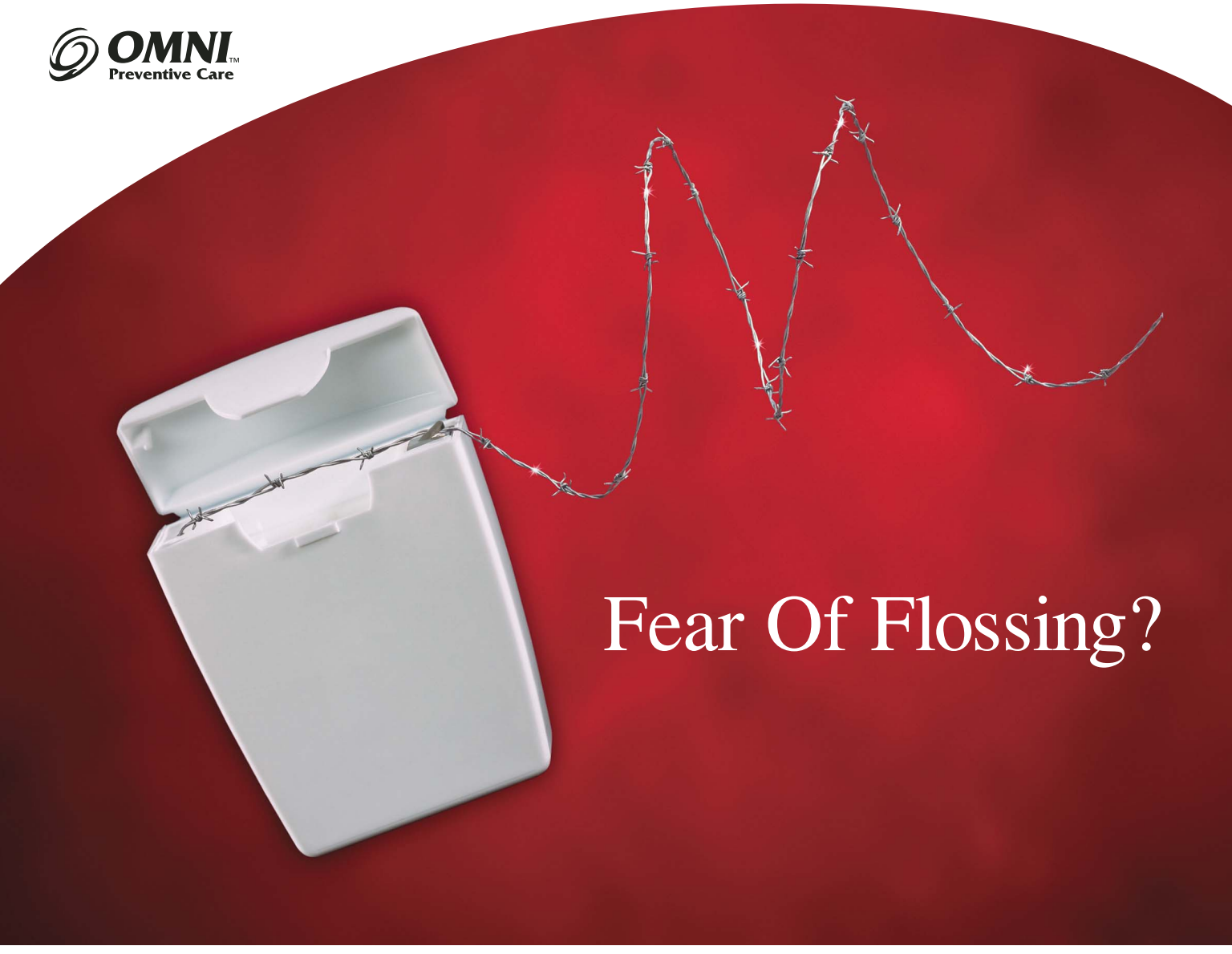

Gingival bleeding? Make sure patients know it's not the floss.

If patients are afraid to floss because their gums bleed, first let them know that it's not the floss that is causing the problem and that daily flossing actually helps improve gum health. Then start the patient on PERIDEX® chlorhexidine gluconate 0.12% therapy, the oral rinse indicated for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding on probing. That's a claim you will not hear from the makers of OTC mouthwashes.

For more information, call 800-445-3386 or visit www.omnipreventivecare.com.

PERIDEX is indicated for use between dental visits as part of a professional program for the treatment of gingivitis. Patients with a known sensitivity to Chlorhexidine Gluconate should not use PERIDEX. The effect of PERIDEX on periodontitis has not been determined. Common side effects associated with the use of PERIDEX include an increase in the staining of oral surfaces, an increase in calculus formation, and an alteration in taste perception. Please see adjacent page for full prescribing information.

PERIDEX® ORAL RINSE
(CHLORHEXIDINE GLUCONATE 0.12%)

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