Osteoporosis: The Disease, Its Controversies, Treatments and Its Complications

Definitions: Osteoporosis literally means porous bone. However, there is a biologic definition and a clinical working definition.

Biologic Definition: The weakening of bone due to thinning of the bone cortex and the trabecular struts between the cortices. This is an age related phenomenon more than an actual disease and is similar to loss of muscle mass and the thinning of scalp hair that is experienced with age.

Clinical Definition: The World Health Organization (WHO) defines osteoporosis via a Bone Mineral Density (BMD) measurement using a dual energy x-ray absorption (DEXA) scan which gives a value in mg/dl or g/dl. This value is similar to the Hounsfield units more familiar to dental practitioners. A diagnosis of osteoporosis is made when the BMD value is 2.5 standard deviations below the arbitrary normal set as the mean BMD of a 22 year old white Caucasian woman. If the BMD value is only from 1 to 2.4 standard deviations below this arbitrary norm, a diagnosis of osteopenia is made. Osteopenia is not considered a disease by the WHO. These standard deviations of the BMD are referred to a T-score. Since T-scores related to osteopenia and osteoporosis are always below the arbitrary norm they are usually minus T scores (i.e. -2.0, -2.5, -3.4 etc). The WHO defines normal as T-scores better than -1 (i.e. -0.5, +1, +1.5, etc.) and osteopenia as a T score between -1 and -2.5. A T-score below -2.5 is considered osteoporosis and an individual with a history of a "fragility fracture" (non-traumatic fracture) and a T score below -2.5 is considered to have severe osteoporosis (Fig. 1).

The Mechanism of Osteoporosis: Bone remodeling is actually bone renewal. Once an osteoblast becomes entrapped in its own mineral matrix to become an osteocyte, it lives for about 180 days[1]. During that life span it prevents resorption

of its mineral matrix by secreting osteoprotegerin (OP) which inhibits the signaling mechanism for osteoclasts to resorb bone.[2] The osteoclast signaling mechanism is a protein called Reactor Activator of Nuclear kappa-b Ligand referred to as RANK-L.[3] It is secreted by the osteoclast itself and sometimes even by osteoblasts. Young osteocytes secrete sufficient amounts of OP to inhibit the resorptive signaling affects of RANKL. However, as osteocytes age toward the end of their 180 day life span known as a Sigma their ability to secret OP declines and RANK-L stimulation tips the scale toward bone resorption (Fig. 2, Fig. 3).[4] In a similar mechanism necrotic bone which secretes no OP is either resorbed or sequestered depending on the amount of necrotic bone present.

New bone formation results directly from this resorption. As the osteoclast resorbs the mineral matrix of bone it releases the bone morphogenetic protein (BMP) and the insulin like growth factors 1 and 2 (ILG-1 and ILG-2) originally embedded into it by the osteoblast which formed the bone (fig. 4).[5] These growth and differentiating factors act upon local resident and some circulating stem cells as well as adjacent osteoblasts to lay down replacement bone. Osteoporosis comes into play because after age 22, this replacement is not 1 to 1 with resorption.

Why is osteoporosis more common in post menopausal women?

This less than 1 to 1 new bone formation after resorption is small but equal between men and women prior to menopause. During and mostly after menopause the rate of BMD decline is much greater in women than in men. This is due to their fall off of estrogen because estrogen is required for osteoblast differentiation.[6] In the absence of estrogen, mesenchymal stem cells and osteoprogenitor cells undergo more lipoblast differentiation. This has been graphically observed in various jaw surgeries and ilium bone harvests for jaw reconstruction as fatty marrow.

What are the epidemiologic Factors Related to Osteoporosis?

In addition to menopause as the most significant factor leading to osteoporosis, genetics, age, activity, (functional bone loading) and nutrition also play a role. Most dental practitioners and orthopedic surgeons who perform surgeries on bone know that some individuals possess a more dense bone then others. The WHO also recognized this related to racial characteristics and sex. That is, individuals of African black heritage are noted to have higher BMD and T-scores than their age matched white Caucasian counterparts and men of any race or culture have higher bone mineral density values than women of the same age and race or culture (Fig. 5).

Bone mineral density declines with age in both men and women of any race. However, the rate of decline is about equal between races and sex until menopause after which the rate of BMD decline is much greater in women of all races (see Fig. 5). Clinical experience suggests that osteoporosis is clinically more common and more significant in white Caucasian women and Asian women although this latter group has not been as thoroughly studied.

Since bone is primarily type I collagen into which calcium hydroxylappetite crystals are placed along with trace amounts of the afore mentioned growth factors, the nutrition supporting bone renewal and therefore resisting osteoporosis centers about protein, calcium, and 25 hydroxy Vitamin D. Therefore, adequate dietary protein must be within the diet itself and supplements of calcium and hydroxy Vitamin D is often recommended. However, one must remember that osteoporosis is a problem more of bone turnover than of mineral content which underscores the limited value of the BMD value itself and of dietary calcium and vitamin D.

There is little doubt that activity also plays a key role as functionally stimulated bone will tend to respond by thickening the cortex and the marrow trabecular network. This is graphically illustrated by our astronauts who lose up to 30% of their bone mass after a prolonged stay in a zero gravity environment but regain

almost all of it with their return to earth's gravity. Dental practitioners also witness this correlation after functionally loading dental implants. In such cases, the trabecular bone density is seen to increase once the implants are restored and is especially evident when the implants are placed into a bone graft (Fig. 6 and Fig. 7).

Treatment Strategies and Drugs for Osteoporosis.

The fundamental goal in treating osteoporosis is prevention of fractures. The two skeletal locations of interest related to osteoporosis factures are the 'spine" which is actually the vertebral bodies and the "hip" which is actually the neck of the femur about the greater and lesser trochanters (Fig. 8, Fig. 9).

Bisphosphonates

The treatment strategy of the bisphosphonates is anti-resorption which sounds very positive upon superficial inspection. That is, preventing resorption should in theory prevent the bone from becoming porous. However, this strategy ignores the known resorption – renewal cycle of bone. It therefore actually reduces new bone formation and leaves old bone in place. A compilation of the Merck Co. sponsored studies and independent studies confirmed a bone strengthening effect for 3 years after which the therapeutic effect of oral bisphosphonates ceases. Recognizing this, the FDA, as of September 2011, recommended stronger warnings in the product label as well as a limitation on the duration of therapy to the manufacturers of oral bisphosphonates.[7] Specifically, they recommended that physicians treating osteoporosis patients re-evaluate them at three years and should consider withdrawing the drug on or before five years. This old bone over time and with long term bisphosphonate use becomes brittle and actually more prone to fracture. This has become apparent to the dental community as bisphosphonate induced osteonecrosis (BIONJ)[8, 9, 10, 11] (Fig. 10, Fig. 11)and to orthopedic surgeons as non-traumatic subtrochantaric fractures of the femur (Fig. 12).[12, 13, 14, 15, 16]

The jaws are the target for exposed bone osteonecrosis because of the fundamental action of bisphosphonates which is to achieve anti-resorption by impairing and mostly killing osteoclasts and their precursors in bone marrow.[17] Because the alveolar bone in the jaws is the most and fastest remodeling bone in the adult skeleton due to dental occlusion and the wearing of dentures, BIONJ always begins in the alveolar bone or the surface of a torus which is another rapidly remodeling bony structure.[18] The mid shaft of the femur is the second area of significant bone remodeling in the adult skeleton because it is the bending moment point during walking. Therefore, the bisphosphonates caused fractures are always located in this unique area which does not experience fractures from trauma which occur mostly at the trochanteric level.[13, 14]

The oral bisphosphonate drugs used to treat osteoporosis are residronate (Actonel or Atelvia) 35 mg/week, Ibandronate (Boniva) 150 mg/month (this averages out to be 35 mg/week) and Alendronate (Fosamax) 70 mg/week (note alendronate is now available as a generic). Each of these is a nitrogen containing bisphosphonate which adds sufficient potency to be used to treat osteoporosis and to cause BIONJ. Each pill is irritating to the esophagus and has a high incidence of esophagitis.[19] This is why individuals are instructed to take the pill with two full glasses of water and to remain upright for an hour. It is also why the initial daily doses of Actonel and Fosamax created such a significant noncompliance that each manufacturer switched to a weekly dose and the introduction of Boniva was a monthly dose. This was later followed by the introduction of Zoledronic acid as Reclast for a once each year intravenous dose, and the even more recent introduction of denosumab as Prolia by a subcutaneous injection.

The intravenous from of Zoledronic acid known as Reclast is the same as the commercial drug known as Zometa administered to limit bony resorption from metastatic cancer deposits in bone and reduce the hypercalcemia of malignancy as an intravenous 4 mg dose monthly.[20] As Reclast, Zoledronic acid is also

administered intravenously to avoid the esophagitis and therefore noncompliance as a 5 mg dose once yearly.[21] Reclast was introduced to the market place in 2008 and has already caused cases of bisphosphonate induced osteonecrosis of the jaws. Its optimal dose overtime and length of therapy has not been stated by the manufacturer.

Denosumab: The strategy for denosumab is the same as that for bisphosphonates. That is, prevention of fractures by an antiresorptive mechanism. Like bisphosphonates denosumab targets the osteoclast and prevents its ability to resorb bone and therefore also prevents new bone formation. Therefore, denosumab has the same down side as the bisphosphonates in retaining old bone which is initially stronger but with time becomes brittle and prone to become exposed jaw bone in the mouth and possibly to cause femur fractures as alendronate is known to cause with long term use. [13, 14]

The commercial preparation of denosumab is known as Prolia. It is a subcutaneous injection of 60 mg once every six months. It was introduced in June of 2010. Like Reclast the optimal length of therapy is not known or stated by the manufacturer. Cases of osteonecrosis of the jaws caused by Prolia have also already been reported.[22]

Prolia's mechanism of anti-resorption and therefore anti-bone renewal is somewhat different than the bisphosphonates. Whereas bisphosphonates are an internal metabolic poison, Prolia is a monoclonal antibody that inhibits RANK Ligand. By doing so it impairs the osteoclast from resorbing bone.

Raloxifene (Evista): Raloxifene commercially marketed as Evista is a selective estrogen receptor modulator or SERM medication.[23] It is not a bisphosphonate and therefore has no esophagitis or other complication associated with swallowing the pill. Evista comes as a 60 mg oral capsule to be taken once daily without

the precautions required of a bisphosphonate. It has not been known to cause osteonecrosis of the jaws or femur fractures. Because it acts on estrogen receptors in bone in a stimulatory manner like estrogen itself it promotes osteoblast differentiation and therefore maintains bone in postmenopausal women in a manner similar to the natural estrogen of premenopausal women.[24] Additionally, Raloxifene acts on the estrogen receptors in breast tissue in an inhibitory manner thus providing somewhat of a preventative measure against invasive breast cancer. This breast cancer preventative aspect has been related as equivalent to the chemotherapy drug Taxotere and has gained FDA clearance of Raloxifene for this benefit as well.[25]

Recombinant Human Parathyroid Hormone 1-34 rhPTH 1-34 (Forteo)

This recombinant protein represents the active amino acid sequence of human parathyroid hormone. Although naturally secreted human parathyroid hormone is known to stimulate osteoclast mediated bone resorption, daily micro doses of 20 micrograms paradoxically stimulates osteoblasts to secrete new osteoid instead. Therefore, rhPTH1-34 is vastly different in its osteoporosis strategy than bisphosphonates and denosumab. While bisphosphonates and denosumab essentially retain old bone, rhPTH1-34 produces new bone. Therefore, it actually increases bone mass not just bone mineral density.[26] As Forteo rhPTH1-34 is subcutaneous injection of 20 micrograms daily. It is FDA approved for three cycles of 28 days each for maximum effect. Its specific FDA approved indications is for "severe osteoporosis: so that it is usually not prescribed for osteopenia or prevention of osteoporosis. It has not been associated with osteonecrosis of the jaws. However, in some animal models high doses and long term use has been associated with cancer development.[27] Although such cancer development has not occurred above background rates in humans, its treatment sequences are limited to three 28 day cycles.

Salmon Calcitonin

Salmon Calcitonin known commercially as Miacalcin or Fortical comes as a nasal spray and a subcutaneous injection each delivering 200 IU of synthetic Calcitonin for a once daily use. As a synthetic of the salmon Calcitonin molecule, it is more potent and has a much longer duration of action than mammalian Calcitonin.[28]

As does native human Calcitonin, the bisphosphonates and the denosumab drugs, salmon Calcitonin has an antiresorptive effect on bone by depressing osteoclast function and reducing their numbers. Therefore, its overall effect is the retention of existing bone at the expense of bone renewal. Salmon Calcitonin differs from the bisphosphonates in one critical area. That is, it does not have the long 11 year half life in bone as do all bisphosphonates.[29] Instead, it is readily metabolized and therefore does not accumulate in bone.

Most importantly is a relatively new warning concerning salmon Calcitonin by the United States Food and Drug Administration (FDA). As recently as April 15, 2013 the FDA published their review of all the safety data related to salmon Calcitonin and identified a small but significant overall increased cancer risk from a background rate of 0.7% to 2.4% (a 3.4 fold increase) with long term use.[30] The FDA recommended limiting salmon Calcitonin to no more than three months and stated that the benefits of salmon Calcitonin did not outweighed the risk of its use in osteoporosis.

Vitamin-D and Calcium: 25-OH vitamin D is the activated form of vitamin D and together with calcium supplements are the mainstay of supplements to treat osteopenia and in some cases of osteoporosis. They are recommended to be taken with all the other osteoporosis medications as well. They are the inorganic building blocks of bone but do not by themselves promote the synthesis of type I collagen which is the organic building block of bone. Therefore, dietary protein intake is as important as vitamin D and calcium. Dietary calcium is usually adequate or close to adequate. The daily requirement of calcium is 1000 mg. The daily requirement of

Vitamin D is 800 IU. The daily recommended intake of protein is 4grams in women and 5 grams in men.

From a bone science perspective one must accept that an age related reduction in bone mass does occur in most everyone. However, in most people, children, young adults, men, women including post menopausal women it does not reach a critical level that causes a fracture without an episode of significant trauma. No doubt many people especially post menopausal women may benefit from osteoporosis treatment. However, the DXA scan generated BMD is only a surrogate test that does not even correlate to fracture risk and measures the wrong thing. Therefore, who will actually benefit from osteoporosis treatment and what treatment is best is largely left up to individual prescribers and the many influences placed upon them. Additionally, bisphosphonates and denosumab represent poor long term strategies to prevent osteoporosis related fractures and alendronate (Fosamax) in particular has actually caused femur fractures and jaw fractures. Raloxifene and rhPTH1-34 represent an improved strategy to treat osteoporosis via drug therapy. However, Raloxifene is less popular than the bisphosphonates and has not been studied or approved to prevent hip fractures. Forteo is limited at this time to severe osteoporosis, leaving bisphosphonates as the mainstay for osteoporosis prevention and treatment with exercise, vitamin D, calcium, and an adequate protein diet as the main alternative. Suffice it to say that fewer individuals actually require drug treatment than are currently receiving it. At this time, the current FDA recommendation of limiting drug therapy to three years after which retesting and a continued treatment is indicated only if the osteoporosis has worsened is a reasonable approach until more definitive data or better long term treatments become available.

Osteoporosis - The Clinical Disease

As a disease entity, osteoporosis today is mired in confusion, controversy, and competition. There seems to be two camps significantly divided as to whether

osteoporosis represents a true disease or an aging process and whether drug treatment or exercise and nutrition are the best at preventing fractures. Those in the camp of drug therapy produce a large number of statistical extrapolations as facts that, if taken as accurate, recommend that osteoporosis begins and occurs in children and develops in men as well as in premenopausal women.[31, 32] Those groups are not traditionally known to suffer from osteoporosis signs or symptoms yet this camp suggests drug treatments for this population as well and therefore for nearly everyone.

Those in the nutrition camp counter by relating that low bone density is an aging process not a disease and use the analogy of skin laxity and a reduction in muscle mass seen in everyone as they age. Their point is also that low bone density does not equate to an increase fracture risk but that low bone quality does instead which undermines many of the drug therapies currently in place.[33]

Both camps are fueled by large revenues tied to each industry. Osteoporosis drugs represent a 17 billion dollar per year market and the exercise nutritional supplement/diet control market an equal amount.

In the middle of this is the public and many of the physicians not committed to either camp and of course, the dental profession which must deal with preventing and treating the continually growing number of cases of what is now referred to by the American Medical Association as Drug Induced Osteonecrosis of the Jaws (DIONJ)[34] that are occurring.

The Case For Osteoporosis Treatment With Primary Drug Therapy

The following statistics have been published by bone and mineral organizations, osteoporosis organizations, and others as well as physician members of such organizations.[35, 36] They are:

1. 50% of women over 50 will suffer an osteoporosis-related fracture in her lifetime
2. Osteoporosis causes 1.5 million fractures every year in the United States.
3. In women age 50 to 59, 58% have low bone mass and this percentage increases each year.
4. In women over 45 years of age, osteoporosis accounts for more days spent in the hospital than many other diseases including diabetes, myocardial infarction, and breast cancer.
5. The national direct expenditures for osteoporosis related fractures are 14 billion dollars each year.
6. Osteoporosis has been called a pediatric disease with geriatric consequences.
7. Over 80% of all fractures in people over 50 are caused by osteoporosis.
8. Twenty eight percent of women and 37% of men who suffer a hip fracture will die within the following year.
9. In the United States today 10 million individuals have osteoporosis and 34 million more have low bone mass, placing them at risk for this disease.
10. More than two million American men suffer from osteoporosis, and millions more are at risk. Each year, 80,000 men have a hip fracture, and one third of these die within a year.

The Case Against Osteoporosis As A Disease And For Nutritional/Diet Therapy Instead

This camp points out the flaws in these statistics and makes the case that treating an arbitrary bone mineral density is the wrong strategy.[37, 38] They report:

1. The United States Surgeon General reports only 17% of women over 50 years of age will develop a hip fracture that the 50% claim comes from incidental radiographic findings of reduced vertebral size unassociated with symptoms but recorded as a fracture.

2. "Low Bone Mass" is not low bone mass at all but low Bone Mineral Density (BMD) measured by the dual energy x-ray absorbitometry (DXA) scan that was actually developed by Merck Co the originators and manufacturer of alendronate (Fosamax) and set the mark of a -2.5 T-score as the firm diagnosis of osteoporosis.[39] They further claim that these so called osteoporosis caused fractures are actually caused by falls and other injuries and that a causal effect from the osteoporosis has not been proven. This claim is supported by a multi-centered European study in the British Medical Journal entitled "Shifting the Focus in Fracture Prevention from Osteoporosis to Falls."[40]
3. The low bone mass as measured by the DXA scan of BMD units in g/dl has been studied by the World Health Organization which found that women's maximum bone mass occurs around the age of 22 years and set this value as normal. However, nearly everyone over the age of 30 will naturally have a lower bone mass than at age 22 and certainly most all women over 50 years will have as well. They further claim that the BMD does not measure bone quality and does not take into consideration vitamin D levels, steroid history, vitamin K levels, muscle strength, activity level, urine PH, and acidifying drinks and diet.
4. Osteoporosis by itself does not require hospitalization, only the fractures do. If falls and other injuries actually cause these fractures, the actual hospital stays cannot be attributed to osteoporosis. Even the length of hospital stays are found to be related to the many comorbid diseases in this age group not the osteoporosis.
5. If the expenditures are 17 billion dollars each year on osteoporosis drugs and the cost of treating fractures is 14 billion dollars it would seem to be nearly equal and once again predicated on the fact that the osteoporosis causes the fractures not falls or other injuries that would fracture a bone regardless of drug therapy. This author (REM) would be in agreement with this as we have followed 104 patients with DIONJ due to oral bisphosphonates and 34

(32.7%) fractured a bone or the jaw due to a fall even though they had been taking an oral bisphosphonate.

6. All diseases can be said to begin in children and adolescents. Heart disease and hypertension in particular have been shown to follow this epidemiology. This should not be the indication to start drug therapy.
7. 80% of fractures in people over 50 years is an estimate and assumes once again that the osteoporosis is the cause of rather than a coincidence in the fracture. This statistic is refuted by another multi-centered randomized prospective unsponsored study out of Europe that appeared in the British Medical Journal.[41]
8. The high rate of death each year after a hip fracture in both men and women is not related to their osteoporosis but due to the comorbidities for the diseases of aging such as heart disease, diabetes, arthritis etc. that caused them to fall in the first place.
9. The large numbers of individuals carrying a diagnosis of osteoporosis and/ or low bone mass is due to the low threshold values of the BMD set by a drug company and later adopted by the WHO. It does not consider bone quality which is protein related, something that the BMD does not measure.
10. If 80,000 men develop hip fractures caused by osteoporosis and one third die each year that would identify that over 26,000 men die each year from osteoporosis. That is, three times more than the deaths from oral pharyngeal cancer, and more than three times those from leukemia, kidney, thyroid, and esophageal cancers among others. This is highly unlikely.

The nutrition/exercise camp instead recommends daily exercise together with calcium, vitamin D and vitamin K supplements along with a normal to high protein diet. They discourage alcohol and highly acidic drinks particularly phosphoric acid containing soft drinks. They embrace the European studies which recommend reducing the probability of falls in those over 50 years of age by:

1. Exercise training
2. Building muscle strength
3. Improve home lighting
4. Reducing sleep medications, antidepressants, and other medications that produce drowsiness
5. Firmly securing carpets and throw rugs
6. Since many fractures occur in the bathroom, add grab bars to shower and bath tub areas, and increase the surface texture of floors to prevent slipping.

Osteopenia/Osteoporosis and the Dental Profession:

The dental profession is indirectly and directly affected by the osteoporosis controversy. While treatment is mostly a matter between these groups with divergent opinions and even data, the dental profession needs to understand the process of bone aging/osteoporosis and the varying treatments in which our patients take. It also needs to be able to understand the medical language concerning osteoporosis and know how to communicate with physicians treating osteoporosis.

More directly it involves the type of bone in which we place dental implants today and of course DIONJ. Related to bone type, most all dental implant placing dentist know that the maxilla in general and the posterior mandible have less trabecular bone density. That it, it is mostly type III or Type IV bone and indeed worsens with age. Therefore, these site locations together with advanced age are associated with a slightly reduced primary stability and a slightly greater implant failure rate. Overcoming this reduced trabecular bone density and even combating periodontal bone loss with the use of bisphosphonates was once of great research interest among periodontal researchers.[42] However, with the identification of DIONJ due to the same bisphosphonates being researched as well as reduction in the manufacturer's sponsorship of such research little or no applications have emerged.

Instead, post menopausal women must accept a slightly higher failure rate if dental implants are placed or undergo a site improvement or site preparation procedure. Today, this may take the form of socket grafting, ridge splitting procedures with grafting, segmental distraction, sinus augmentation or horizontal or vertical ridge augmentation using the providers preferred grafting material.

Drug Induced Osteonecrosis of the Jaws (DIONJ)

Today, most every dental professional is aware of jaw osteonecrosis caused by IV and oral bisphosphonates and more are becoming aware of cases caused by denosumab. Drug induced osteonecrosis of the jaw was first introduced to the dental and medical profession in the textbook: Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment by Marx and Stern 2002.[43] The first scientific literature publications occurred in September of 2003[44] with two more following by the end of that year.[45, 46] Now a decade later, two textbooks, and over 1400 publications have appeared relating over 15,000 DIONJ cases attesting to the epidemic proportions predicted in the first publication.[44] Today, dental professionals must be keenly aware of the mechanism of DIONJ, the risks of precipitating it as well as prevention and treatment measures in the patients treated for osteopenia and/or osteoporosis.

The current drugs that place osteopenia and osteoporosis patients at risk for DIONJ are the oral bisphosphonates, alendronate (Fosamax and generic equivalents), Residronate (Actonel and Atelvia) and Ibandronate (Boniva); the subcutaneously injected denosumab (Prolia); and the intravenous bisphosphonate Zolendronate (Reclast). All of them impair osteoclastic bone resorption and therefore bone renewal thereby retaining old bone and reducing its ability to turnover. Because the alveolar bone in the jaws turnover faster and more than any other bone in the adult skeleton[47] it is the focal point for DIONJ from these drugs.

Of the oral bisphosphonates, alendronate is the drug linked to 96% of cases of DIONJ from an oral bisphosphonate as compared to residronate 3% and Ibandronate 1%.[48] This is mostly due to the fact that the alendronate is marketed at twice the dose of all other bisphosphonates (70mg/week) while it has the same absorption, distribution, and the same potency of the others. Although Zolendronate as Reclast is new and is given 5 mg IV only once yearly for osteoporosis it has already caused several cases of DIONJ in this authors experience. This is because the half life in bone of 11 years is the same for all the bisphosphonates[29] and the IV infusion loads the bone 140 times more than any oral bisphosphonates.[48] Therefore, dental professionals must realize that although some DIONJ cases may occur sooner, the significant DIONJ risk for an oral bisphosphonate begins at about 3 years of weekly dosing and with IV Reclast at about the fourth yearly dose. Needless to say, those osteopenia/osteoporosis patients converted to Reclast after taking an oral bisphosphonate are at risk for DIONJ before the fourth dose.

Denosumab (Prolia) as a RANK Ligand inhibitor does not seem to bind to bone or to accumulate in bone as do bisphosphonates. Therefore, discontinuation as a "drug holiday" becomes a useful tool for the clinician in this drug as it does in oral bisphosphonates. Drug holidays are useful in patients taking oral bisphosphonates because only 0.64% of any oral bisphosphonate is absorbed through the intestines into the circulation.[19, 20, 49] This amounts to a slower accumulation in bone and a gradual toxic death to osteoclasts. Therefore, the bone marrow is able to replace lost osteoclasts to some degree and remains able to repopulate the osteoclast population during a drug holiday.

Prevention – What to Do and What Not to Do:

Dental professionals are well to note that these anti-osteoclastic drugs when given to adults do not become bound into tooth structure. Therefore, caries removal, restorations, crown and bridge, nonsurgical root canal therapy as well as dental

prophylaxis, removable partial and full dentures are safe to perform at any time. In fact, it is advisable to accomplish these more preventative dental procedures in these patients so as to prevent the need for alveolar bone surgeries in the future. What is to be avoided is deferring needed dental care or neglecting it because of the intimidation of DIONJ.

For the patient requiring a surgery within the alveolar bone (tooth removals, alveoloplasty, dental implants, osseous periodontal surgery, apical resective root canal therapy) and who has taken an oral bisphosphonate or Prolia for less than three years it is reasonable to assess the bone turnover suppression by requesting a morning fasting serum c-terminal telopeptide (CTX) test. Several studies have shown that a value of 150 pg/ml or greater is consistent with alveolar bone healing.[50, 51, 52] In such cases where the CTX test is above 150 pg/ml, the planned alveolar bone surgery can be accomplished and a three month drug holiday requested from the prescribing physician to cover the healing period. If the CTX value is below 150 pg/ml it is advisable to request a drug holiday from the prescribing physician prior to accomplishing the planned alveolar bone surgery. The length of the drug holiday will depend on the drug dose and the length of time the patient took the drug. Most patients taking these drugs for less than three years will either return a CTX value above 150 pg/ml initially or require a short drug holiday of three months or less to gain a value above 150 pg/ml.

For patients who have taken an oral bisphosphonate or Prolia for more than three years the initial CTX is usually below the 150 pg/ml level. For such patients a longer drug holiday is usually necessary and many are required to be as long as nine months. If the practitioner has no access to obtain a CTX serum test or the patient declines it, this author has found that an arbitrary nine months to one year drug holiday will gain alveolar bone healing after a surgical procedure in most all cases.

For urgent surgeries in the alveolar bone such as painful abscesses, bone fractures vertical root fractures etc it is better to accomplish the needed surgery and request a drug holiday for the following three months than to allow the problem to further damage bone that may very well initiate osteonecrosis is such patients. Of course, an informed consent outlining a greater risk for developing DIONJ due to the urgent need for alveolar bone surgery in the face of bone healing compromised by these drugs is advisable.

A special note about the CTX Test:

Despite three peer reviewed studies documenting the clinical utility of a properly performed CTX test[50, 51, 52] as well as the use of the CTX or NTX test in most all of the oral bisphosphonate drug company sponsored research studies,[53, 54] the value of this test for oral surgical procedures remains controversial. It is curiously missing from the position papers of the American Association of Oral and Maxillofacial Surgeons,[55] the American Dental Association,[56] and the American Society of Bone and Mineral Research.[57] This likely due to several misapplications of the CTX and misunderstandings of what is actually tested and what can interfere with its accuracy.

The CTX test measures an eight amino acid sequence derived from collagen when the osteoclast resorbs bone. Its name CTX comes from the fact that this amino acid sequence is derived from the carboxy terminal end of collagen hence its designation CTX. A less consistent serum test from the amino terminal end of collagen is termed the NTX and is a lesser used alternate test.

Some of the misapplications arise from the fact that cancers split off collagen fragments that cross react with this test resulting in abnormally high values. Therefore, using the CTX in cases of IV bisphosphonate ONJ cases where the bisphosphonates was prescribed for treating metastatic cancer deposits in bone or

for hypercalcemia of malignancy is inappropriate and detracts from its valid use in noncancerous patients. Additionally, patients who have received methotrexate which inhibits bone marrow stem cells and/or steroids which inhibit collagen synthesis will cause CTX values to be falsely low. This is due to the reduction of collagen in bone. Therefore, the CTX is not to be relied upon in such patients. One other phenomenon may also be noted. That is, patients beginning a drug holiday after seven or more years of an oral bisphosphonate will begin with very low CTX values followed by a rise as the drug holiday progresses. However, a paradoxical decrease in the CTX value may be seen as the drug holiday progresses further. This is due to a recovery of the bone marrow osteoclast precursors which produces osteoclasts that begin resorbing bone. As they do, they die off and rupture releasing the unmetabolized bisphosphonate with its high affinity for bone. The released bisphosphonate then is taken up by the bone again, suppressing the CTX value. However, a nine month to one year drug holiday will return alveolar bone healing in these individuals.

Diagnosis and Treatment:

An updated definition for Drug Induced Osteonecrosis of the Jaws can be derived from the definitions used by most dental associations for Bisphosphonate Related, Bisphosphonate Induced, or Bisphosphonate Associated Osteonecrosis of the Jaws as: *Exposed bone in the maxilla or mandible in a patient receiving a systemic antiresorptive drug that fails to heal over eight weeks and who has not received radiotherapy directly to the jaws.* About 50% occur spontaneously with the remainder resulting after a trauma to the jaws, usually a tooth removal or other alveolar bone surgery. About 50% will also occur in the lingual cortex in the molar region of the mandible. This has been attributed to the axial loading forces being directed on this cortex and to the increase forces on molar teeth during occlusion (Fig. 13).

Staging of DIONJ:

Previous staging systems for ONJ have incorrectly included pain as a major contributor to staging. Since pain in DIONJ is due to secondary infection, it changes with antibiotic therapy, the patient's pain tolerance and the day to day activity of the secondary infection. Since any staging system should indicate the severity and extent of the disease regardless of subjective pain the following staging system is the most appropriate:

Stage I: Exposed bone limited to one quadrant

Stage II: Exposed bone involving two quadrants

Stage III: Exposed bone in three or four quadrants or osteolysis to the inferior border or a pathologic fracture or extension into the maxillary sinus

Treating DIONJ in the osteopenia/osteoporosis patient

The exposed bone represents necrotic bone. If the offending drug is continued the area of exposed bone is likely to increase and secondary areas of exposed bone may develop. It is advised to request a drug holiday from the prescribing physician. It is cautioned that the dental practitioner should refrain from instituting the drug holiday directly as osteoporosis therapy is not within the scope of any dental specialty. Studies have shown that a drug holiday of nine months will result in a spontaneous sequestration and exfoliation of the exposed bone followed by mucosal healing in 50% of cases (Fig. 14 and Fig. 15).[48] These cases are usually the smaller areas of exposed bone. During this drug holiday clinicians find it useful to use 0.12% chlorhexidine oral rinses three times daily to prevent secondary infection. If a secondary infection does develop penicillin VK 500 mg four times daily or if the patient is penicillin allergic, doxycycline 100 mg once daily are the best antibiotics to use.

In the 50% of cases where the exposed bone does not exfoliate with a drug holiday a surgical debridement after a drug holiday of nine months or a CTX value greater than 150 pg/ml has been associated with resolution of the DIONJ (Fig.'s 16, 17,

18, 19).[48] It should be noted that such drug holidays and debridement surgeries are not predictable and often not successful in the cancer patients treated with IV bisphosphonates or sub cutaneous Xgeva due to the 11 year bone half life of the bisphosphonates coupled with the 140 times greater bone loading via the IV route and the high dose of denosumab in Xgeva.

Longer term use of oral bisphosphonates, especially alendronate, with or without comorbidities may result in extensive osteonecrosis (Stage III). In the mandible this may require a mandibular resection (Fig.'s 20, 21, 22, 23, 24, 25) and in the maxilla an alveolar resection anteriorly Fig.'s 26, 27, 28, 29, 30) and an alveolar resection together with a sinus debridement posteriorly (Fig.'s 31, 32, 33, 34, 35). In each procedure a nine moth drug holiday followed by another three month drug holiday during the healing course has been shown to predictably resolve the DIONJ. In cases where the CTX rises above 150 pg/ml prior to nine months the indicated surgery may be accomplished at that time with predictable healing.

It is extremely rare that a prescribing physician will disagree with a drug holiday. In such a situation the dental team may suggest the alternatives of vitamin-D together with calcium, and protein or Raloxifene or rhPTH1-34 as an alternative. Additionally, the author (REM) will refer the physician to the sentinel article by Black DN, Schwartz, Ensrud et al [58] that appeared in the Journal of the American Medical Association December 26, 2006. In this multicentered randomized prospective study discontinuation of the bisphosphonate for 5 years did not result in an extension or worsening of osteoporosis. In the dental utility of drug holidays for one year or less to treat or prevent DIONJ, it is well within the proven safety toward the patient's osteoporosis.

Once a DIONJ in the osteopenia/osteoporosis patient is resolved bony reconstruction of the lost bone is feasible by the usual and individually preferred methods of the practitioner. Where there remains sufficient bone to accommodate

dental implants, dental implant placements can be safely accomplished in these patients as in any other patient provided the patient is not restarted on one of the drugs discussed in this chapter known to cause DIONJ (See Fig.'s 16, 17, 18, 19).

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Figure Legends

Fig. 1 The World Health Organization's bell curve defining normal, osteopenia, osteoporosis, and T-scores.

Fig. 2 RANK Ligand concentrations above that of osteoprotegerin stimulates osteoclasts to resorb bone.

Fig. 3 Bone resorption by several osteoclasts recognizing decreased osteoprotegerin secretion from old bone at bottom but unable to resorb younger adjacent bone due to its higher level of osteoprotegerin secretion.

Fig. 4 Resorption of the bone mineral matrix releases the growth and differentiation factors to regenerate new bone.

Fig. 5 The World Health Organization's graph of declining bone mineral densities related to age, sex, and race.

Fig. 6 Less future graft prior to the functional loading from dental implants.

Fig. 7 Increased graft density seen after loading implants with an overdenture.

Fig. 8 Compression fractures of the vertebral bodies called spine fractures are attributed to osteoporosis.

Fig. 9 Hip fracture from trauma occur at the trochanteric level. Many are thought to be predisposed to such fractures form osteoporosis.

Fig. 10 Bisphosphonate induced osteonecrosis of the mandible.

Fig. 11 Bisphosphonate induced osteonecrosis of the maxilla.

Fig. 12 Mid shaft of femur (subtrochantaric) fracture caused by Alendronate (Fosamax).

Fig. 13 The axial loading from molar occlusion on the mandible is directed toward the lingual cortex resulting in a site of predilection for drug induced osteonecrosis in the osteoporotic patient.

Fig 14 Exposed bone due to 5.5 years of alendronate (Fosamax) therapy for osteopenia.

Fig. 15 Resolution of exposed bone seen in figure 14 correlated to a nine month drug holiday and rising CTX values.

Fig. 16 Exposed bone representing bisphosphonate induced osteonecrosis due to alendronate (Fosamax).

Fig. 17 A minor office based debridement removed the exposed bone after a nine month drug holiday at a CTX value over 150 pg/ml.

Fig 18 Implant placement into are of previous bisphosphonate exposed bone.

Fig. 19 Successful implant placement and long term outcome (5 years follow-up) due to implant placements after a nine month drug holiday or a CTX value above 150 pg/ml.

Fig. 20 Exposed necrotic bone in the mandible representing bisphosphonate induced osteonecrosis.

Fig. 21 Necrotic bone form bisphosphonate induced osteonecrosis often become secondarily infected. In this case two cutaneous fistulas developed.

Fig. 22 A hemimandibulectomy was required to resolve this case of bisphosphonate induced osteonecrosis.

Fig. 23 Resolution of exposed necrotic bone and healing of mucosa after surgery.

Fig. 24 Resolution of cutaneous fistulas after surgery.

Fig. 25 A long span titanium plate was used initially to reconstruct the resultant continuity defect and has been stable for 4 years.

Fig. 26 Bisphosphonate induced osteonecrosis of the maxilla limited to the alveolar bone.

Fig. 27 Necrotic bone removed after a drug holiday of nine months and a CTX value over 150 pg/ml.

Fig. 28 The resultant alveolar defect was grafted with in-situ tissue engineering principles using Platelet Rich Plasma (PRP), recombinant human Bone Morphogenetic Protein (rhBMP-2/ACS) and Crushed Cancellous Freeze Dried Allogeneic Bone (CCFDAB).

Fig. 29 Healed site of resolved osteonecrosis with provisional appliance made to avoid pressure on graft site.

Fig. 30 Fully regenerated alveolar ridge from insitu tissue engineered graft.

Fig. 31 Stage III bisphosphonate induced osteonecrosis of the maxilla.

Fig. 31 After a nine moth drug holiday and a CTX level above 150 pg/ml a bony debridement and aggressive removal of secondarily infected sinus membrane was accomplished.

Fig. 33 Teeth, necrotic bone, and infected sinus membrane from debridement surgery.

Fig. 34 To assist the healing advancement of the buccal fat pad with its robust blood supply before a primary mucosal closure is advised.

Fig. 35 Healed surgical site and resolution of the osteonecrosis and sinusitis.