# Incidence of Osteonecrosis of the Jaw Not Associated with Anti-Resorptive Medications

by

Vandana Singh

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Medical Sciences-Oral Medicine

University of Alberta

## Abstract

**Objectives:** Since 1993, there have been multiple case reports and small case series describing the apparently spontaneous occurrence of oral mucosal ulcers with a necrotic bone base, involving the posterior lingual mandible or exostoses, in patients not using anti-resorptive medications. Currently, this is referred to as oral ulceration with bone sequestration (OUBS). However, there have been no systematic studies and the incidence and significance of the condition is controversial. The aim of this study was to determine OUBS incidence and characteristic features in patients presenting in general dental practices.

**Methods:** This was a clinical non-interventional cross sectional survey study involving the entire population of general dental practitioners (GDPs) in Alberta. A one-page survey was developed to determine characteristic features and incidence of OUBS as extrapolated from the number of patients in the care of respondents. The respondents were asked to provide an informed response after completing an educational exercise regarding the nature of the condition. To minimize notoriety bias, respondents were specifically requested to respond in the event they had never seen any OUBS cases. Further, respondents were asked to indicate only definitive cases in known patients not receiving anti-resorptive medications. There were at least two subsequent reminders published in the provincial newsletter.

**Results:** 391 responses were accumulated representing about 20% of all active GDPs with a mean practice size of 1736 (SD=105). By extension, this represented the informed observations of about 685,000 (17% of the provincial population). Overall, 51 GDPs (13 %) had seen the OUBS condition at some point in their career. This number increased

with years of practice experience reaching 22% of GDPs after 20-40 years. A total of 113 cases were described. There was a high predilection for lingual mandible (78%), including mandibular tori. Overall, 54% of cases involved the mandibular or palatal tori. 20 cases (18%) had been seen in the last 2 years, which represented a yearly incidence of 0.0015% or approximately 1 new OUBS case per year per 68 thousand patients not receiving anti-resorptive medications. This, in turn, corresponded to a 2.5% chance each year that a GDP serving this provincial population will see the condition. All cases resolved either spontaneously (77%) or following conservative management (23%). 68 % of cases persisted beyond 8 weeks before resolving.

**Conclusions:** This data set represents the first systematic attempt to characterize OUBS presentation and assess incidence. OUBS is an unusual condition, occurring at an estimated 0.0015% yearly incidence in Alberta. This corresponds to about a 2.5% chance each year that a GDP will encounter the condition. Resolution occurred in all cases.

## Preface

This thesis is an original work by Vandana Singh. The research project received ethics approval from the University of Alberta Health Research Ethics Board-Health Panel for the following application: “Incidence and prevalence of osteonecrosis of the jaw not associated with anti-resorptive medications” Pro00066133, 30/10/2016.

## Acknowledgment

My deepest gratitude goes to my family, my parents and father-in-law, for their unconditional love and support for my pursuit of advanced education.

I am forever appreciative to my husband, Jai Singh for his endless care, support, love and motivation throughout this journey. Thank you to my children, Medha and Rishabh, for always being understanding.

I am thankful to my supervisor, Dr. Edmund Peters, for his mentorship, encouragement, guidance and support. To my advisory committee members, Dr. W.T McGaw and Dr. Steven Patterson, this project would not have been possible without your invaluable advice and participation. Thank you for being my inspiration.

Lastly, I would like to acknowledge and thank Dr. Aliya Khan for her comments and support of this project. Also, I would like to thank Dr. James Yacyshyn for his assistance in facilitating access to Alberta dentists in the completion of the survey.

## Overview



## Table of contents

## List of Tables

## List of Figures

## List of Appendices

## 1. Introduction

Osteonecrosis of the jaw (ONJ) was first reported in association with use of bisphosphonates (BP), an anti-resorptive bone medication, in 2003 (1). These early reports described the development of exposed non-vital bone in the oral cavity, primarily in cancer patients on high dose intravenous BP. The lesions were associated with significant morbidity and proved very difficult to manage (2). Since that time, there have been numerous studies and publications, which have attempted to define the etiopathogenesis, epidemiology and management issues of ONJ associated with BP use. In recent years, ONJ cases associated with other forms of anti-resorptive bone medications, such as Denosumab, have been published and the condition is now called medication related osteonecrosis of the jaw (MRONJ). The widely accepted MRONJ case definition, published by The American Association of Oral & Maxillofacial Surgeons (AAOMS) requires the presence of exposed bone for greater than 8 weeks in patients who have been treated with anti-resorptive medications and with no history of radiotherapy (3).

MRONJ in cancer patients receiving IV bisphosphonates has been variably estimated between 1% to 10% and represents the large majority of reported cases, including those with the most significant morbidity (3). The relationship of oral bisphosphonates used in the management of osteoporosis to MRONJ has been more controversial. MRONJ incidence in patients using oral bisphosphonates has been estimated between 0.0004% and 0.06% (4). However, the AAOMS has expressed concern that the reported incidence in patients using oral bisphosphonates has been underestimated (3). This concern is supported by some studies. Data from a single

institution showed 9 active MRONJ cases in 208 patients receiving Alendronate, suggesting a 4% prevalence (5). The authors indicated they did not find a single case of osteonecrosis in a control group of 13522 patients including 4384 who had undergone dental extractions. A further study in 11 clinical centers over a 4 -year period identified 37 MRONJ cases associated with oral bisphosphonate use; 57% of these cases developed spontaneously (6). On a more skeptical note, other recent reviews have concluded there is insufficient evidence to support a causal association and there have been suggestions that the risk is comparable with the general population (7,8). In a recent systematic review published by Kim et al in 2017, they stated that “overall positive predictive value of the algorithm currently used to identify MRONJ is very low, indicating low validity and possible overestimation of ONJ occurrence.” (9). There is general agreement regarding the continuing need to clearly delineate the MRONJ incidence in patients treated for osteoporosis with oral anti-resorptive medications (2-8,10).

A problem with all of the incidence studies, which pre-emptively assigned a primary causal relationship to MRONJ pathosis and anti-resorptive medication is the possibility that patients can show the qualifying clinical parameters for the MRONJ diagnosis in the absence of anti –resorptive medications. This possibility was suggested by early reports of exposed bone, presenting for greater than 8 weeks in patients, who did not use anti-resorptive medications. This was initially reported in 1993, before the availability of anti-resorptive medications, as “lingual mandibular sequestration with ulceration” (11). Since this initial publication there have been multiple other case reports (12-19) and the condition has subsequently been called “spontaneous sequestration” and most recently “oral ulceration with bone sequestration(OUBS)” (20). These reports have indicated a

predilection for OUBS to present in the posterior lingual mandible or in association with exostoses. The clinical similarity of OUBS to MRONJ was noted by Woo et al (2) who suggested this condition appeared to represent a mild form of MRONJ.

The International Task force on Osteonecrosis of the jaw (ITFOJ) in their 2015 consensus statement have agreed with the concept that bone necrosis may occur in the absence of anti-resorptive therapy (4). However, the ITFOJ indicated, in the absence of data, that they feel that oral ulceration and bone sequestration (OUBS) is not associated with significant morbidity and is uncommon even though the incidence of OUBS in the general population is not defined. The ITJOF summarizes this condition as follows:

- The condition occurs as painful ulceration generally involving the posterior lingual mandible at the level of mylohyoid ridge or over oral exostoses. The ulcer can persist for weeks to months.
- It occurs in absence of systemic disease or anti-resorptive therapy.
- Pathogenesis of this condition is not well understood. Ulceration, resulting from trauma or other means such as aphthous ulceration, is thought to be the initial pathogenic event. Sequestration occurs due to disruption of blood supply from the periosteal layer to the vascularized superficial cortical layer. It is usually a self-limiting condition or will resolve with conservative management.
- The concept that these conditions might represent an initiating event for some MRONJ cases is supported by observations that about 25% to 57% of MRONJ cases appear spontaneous which is similar to the OUBS presentation. Further, many MRONJ cases involve lingual mandible or can be associated with exostoses which are the same site predilections indicated by the OUBS case reports.

The review emphasized the need for studies that can evaluate the incidence of this condition (4).

This possible relationship has been challenged by one group of authors, who in a published letter have suggested the OUBS condition is rare and poorly defined with questionable relevance to MRONJ pathogenesis (21). In this regard, it is correct that in spite of multiple case series and case reports, incidence and prevalence studies have not been done. However, it is important to understand that there has not previously been an impetus to collect epidemiologic OUBS data. This is because the condition is either self-limited or can be managed conservatively. To further illustrate this point, traumatic oral ulcers are common but incidence studies are rare or not available because there is no compelling reason to perform such studies. In any event, cautionary notes to this dismissive commentary are available. First, the presenting OUBS features appear well understood and consistent descriptions of the condition are indicated in multiple publications (11-19). Further, in response to selected OUBS reports, there have been other published letters and even an insightful editorial, which suggest OUBS type cases might be common (18,19,22). Of possible additional relevance, a study of bone biopsies obtained from asymptomatic edentulous ridges in patients, not receiving anti-resorptive medication, indicated non-vital bone could be identified in 35% of cases (23).

The foregoing suggests the susceptibility of the jaws to necrotic bone development, even in the absence of anti-resorptive medication and indicate further study is needed. In summary, the incidence of the non-drug associated, exposed jaw bone sequestrations and the fraction of these conditions which persist past the 8 week qualifying window for

the MRONJ diagnosis is not known. However, the clinical similarities between OUBS and MRONJ suggest a possible relationship, including the possibility that OUBS is an initiating event for MRONJ. In this concept, the anti-resorptive medication is suggested to exacerbate, prolong and impair healing of a primary OUBS event. OUBS needs to be more comprehensively characterized to assess this possibility. Currently, there is no data to indicate the incidence of OUBS and our understanding of site predilection and range of duration is based on a limited number of case reports or small case series.

### 1.1 Aim

The aim of this study was to determine the characteristic features of OUBS and OUBS incidence in patients presenting in general dental practices in Alberta.

**Hypothesis:**

Oral ulceration with bone sequestration has a predilection for the same sites as MRONJ and can persist beyond the 8 week qualifying period for the MRONJ diagnosis.

### 1.2 Research Questions

1. Does OUBS have an association with:
    a. anatomic site?
    b. Exostoses?
2. What proportion of OUBS cases persist past 8 weeks?
3. What is the incidence of OUBS in patients presenting in general dental practices?

## 2. Literature review

### 2.1 Preamble:

The literature review focuses on those issues, which are related to bone viability and the clinical consequences when this is compromised. Thus, the review addresses the microanatomic structure of bone with specific reference to vascularization, osteoblasts and osteoclasts with emphasis on their role in bone turnover and re-modelling and the effect of anti-resorptive medications on these cells. Subsequently, suppurative or bacterial osteomyelitis is discussed. This is because one of the defining features of this well-known condition is the development of sequestration or necrotic bone and thus, there is obvious overlap with osteonecrosis, which refers to necrotic bone and has been separately defined as a clinical pathologic entity. Lastly then, the literature on osteonecrosis is reviewed including MRONJ and ONJ which occurs in the absence of anti-resorptive medications (OUBS).

### 2.2 Microanatomic bone structure:

Bone is the structural element of the skeleton. It provides support, allows movement and protects vital organs. It also mediates mineral homeostasis, acts as a reservoir for a range of cytokines and provides the environment for hematopoiesis within the marrow spaces (24). It consists of 50-70% mineral (hydroxyapatite, carbonate, magnesium and acid phosphate), 20-40% organic matrix, 5-10% water and <3% lipids. The mineral component provides mechanical rigidity and load bearing strength whereas the organic matrix provides elasticity and flexibility. The matrix is comprised primarily by Type 1 collagen and is called osteoid. The vascularized mineralized and un mineralized

matrix supports populations of osteoblasts, osteocytes and osteoclasts, Osteoblasts synthesize osteoid and mediate mineralization. Osteocytes are similar but are relatively inactive cells. These cells are found within bone tissue whereas the osteoblasts typically populate the bone surface (24). Osteoclasts are multinucleated cells which resorb bone. These cells are discussed more comprehensively later in this review.

Bone has a dense outer cortical surface (bone cortex) which is covered with a fibrous connective tissue sheath called the periosteum. The peripheral aspect of the dense bone cortex is vascularized by vessels entering from the periosteum. The periosteum is not present at joints where bone is capped by articular cartilage. The periosteum is tightly attached to the cortex by thick collagenous fibers called Sharpey's fibers, which extend into the underlying bone (25). The subsurface structure is formed by interconnecting bone plates called trabeculae and the spaces between the trabeculae are occupied by the highly vascular hematopoietic (marrow) tissue, which includes varying proportions of adipose tissue. The endosteum is a membranous structure which covers the internal bone structures including the trabeculae.

The cortex is formed by bone layers in association with cylindrical lamellated structures called osteons or Haversian systems. The cylindrical Haversian systems form a vascularized branching network within the cortical bone (26). Cortical bone has a porosity less than 5%, which is affected by the proportion of the actively remodeling Haversian systems to inactive Haversian systems.

Both, mature trabecular bone and cortical bone show a lamellar pattern in which collagen fibers are laid down in an alternating orientation. Lamellar bone is best seen during microscopic examination with polarized light. Lamellar bone has significant

strength due to the alternating orientations of collagen fibrils. The lamellar pattern is absent in woven bone, which is produced during formation of primary bone and can also be seen in pathologic conditions with high bone turnover such as hyperparathyroidism and Paget's disease.

The cell populations which mediate bone growth and turn-over are the previously-noted osteoblasts, osteocytes and osteoclasts, which are separately discussed next.

**2.2.1 Osteoblasts and osteocytes:**

Osteoblasts synthesize collagenous organic matrix and regulate mineralization of matrix by releasing small membrane bound matrix vesicles that concentrate calcium and phosphate. They also destroy mineralization inhibitors such as pyrophosphate or proteoglycans.

Osteoblasts arise from the differentiation of mesenchymal cells that arise from osteoprogenitor cells in the periosteum. Osteoblasts form closely packed sheets on the surface of the bone from which they extend their cellular processes through the immature bone. They produce enzymes, growth factors and hormones such as alkaline phosphatase, collagenase TGF B, IGFs, osteocalcin and Type 1 collagen (27). Once the bone forms, osteoblasts become flattened and line the surface or alternatively are lost through apoptosis. When the new bone is deposited, osteoblasts gradually become surrounded by bone matrix and eventually become trapped in spaces called lacunae. These cells are called osteocytes. They communicate with each other via their cytoplasmic extensions that occupy canaliculi within the bone matrix (28). Osteocytes express multiple matrix proteins that support intercellular adhesion and regulate

exchange of mineral in the bone fluid within lacunae and the canalicular network. The cells can transduce stress signals from bending or stretching of bone, which influences this metabolic activity. Osteocytes can undergo apoptosis in response to disruption of cell and matrix interaction (29,30).

**2.2.2 Osteoclasts:**

Osteoclasts are multi-nucleated cells that cause bone resorption. They are derived from the bone marrow mononuclear precursor cells of the monocyte-macrophage lineage (31). RANKL (Receptor activator of nuclear factor kappa-B ligand) and macrophage CSF are two cytokines that are critical for osteoclast formation and are produced by marrow stromal cells and osteoblasts.

RANKL is also known as tumor necrosis factor ligand superfamily member 11 (TNSF 11), osteoprotegerin ligand and osteoclast differentiation factor. RANKL is important for the osteoclast formation. Macrophage CSF is required for the proliferation, survival and differentiation of osteoclast formation (25).

Bone resorption depends on osteoclast secretion of hydrogen ions. Active osteoclasts also secrete acid phosphatase, cathepsin, matrix metalloproteinase 9, gelatinase and cathespin K enzyme. $H^+$ ions acidify the resorption area to dissolve the mineral component of bone matrix. Enzymes such as cathespin K bind to bone matrix via integrin receptors in the osteoclast membrane linking to bone matrix peptides and digests the proteinaceous matrix (25, 31).

Thus, interference with the development or function of osteoclasts will interfere with remodeling or repair activity and promote retention of bone matrix.

**2.3 Bone growth and remodeling:**

Bone undergoes constant growth, modelling and remodeling during life. Longitudinal growth occurs at the growth plates where cartilage proliferates in the epiphyseal and metaphyseal plates. These undergo mineralization to form primary new bone (25).

Remodeling is the process through which bones change their overall shape in response to physiologic or mechanical influences leading to gradual adjustment of the skeleton. This adaptation may be due to deposition or removal of the bone by osteoblasts and osteoclasts respectively. Bones widen with aging due to apposition of new bone and resorption of the endosteal bone (32). This is a process by which bone is renewed to maintain bone strength and mineral hemostasis. It involves continuous removal of old bone and replacement with newly synthesized proteinaceous matrix and mineralization of the matrix to form new bone. Remodeling continues throughout the life span and increases with age (25). The remodeling cycle is composed of three phases: resorption, reversal and formation. Remodeling is targeted to sites that require repair. Activation involves recruitment of monocyte-macrophages, which fuse to form multinucleated preosteoclasts. Osteoclast formation, activation and resorption is regulated by the ratio of RANKL to osteoprotogerin, IL-1, IL-6, colony stimulating factor, parathyroid hormone calcitonin and 1,25 di-hydroxyvitamin D. Osteoclast-mediated bone resorption takes approximately 2-4 weeks (31). The process involves release from osteoclasts of hydrogen ions to lower the pH to 4.5 to mobilize bone mineral. The previously noted enzymes digest the organic matrix, forming saucer shaped Howship's lacunae on the bone surface (25). In the reversal phase, bone resorption transitions to bone formation. Resorption cavities

contain a variety of mononuclear cells such as monocytes, lymphocytes, mesenchymal stem cells and hematopoietic progenitor cells that are recruited to begin new bone formation. The reversal phase has also been proposed to be mediated by strain gradient in the lacunae. This strain gradient may lead to activation of osteoclasts and osteoblasts (25,31)

In summary, bone is internally vascularized from vessels in the medullary spaces and externally vascularized from vessels in the periosteum entering the dense bone cortex. Thus, disruption of the periosteum will cause ischemia in the peripheral aspects of the bone cortex, which in turn can result in bone necrosis. Any factors which impede the function of osteoclasts or osteoblasts will impede reparation or remodeling as well as resolution of bone necrosis.

**2.4 Anti-resorptive medications:**

Anti-resorptive agents are used for prevention of metastasis in patients with malignancies and management of osteoporosis, hypercalcemia, and Paget's disease.

There are five classes of anti-resorptive agents:

1. Bisphosphonates
2. Estrogen
3. Selective estrogen receptor modulators
4. Monoclonal antibodies (Denosumab)
5. Calcitonin

Bisphosphonates and monoclonal antibodies are the two classes which are commonly associated with ONJ and will be discussed in this review.

### 2.4.1 Bisphosphonates:

Bisphosphonates (BPs) are chemical derivatives of inorganic pyrophosphate (PPi). Inorganic pyrophosphate has two phosphate groups which are linked by esterification. Inorganic pyrophosphate is released as a byproduct in many synthetic reactions in the body (33). Earlier studies demonstrated that inorganic pyrophosphate was capable of inhibiting calcification by binding to hydroxyapatite crystals. This led to the hypothesis that regulation of inorganic pyrophosphate levels could regulate bone mineralization (34).

The binding and retention of BPs to hydroxyapatite crystals depends on the availability of hydroxyapatite binding sites. The ability of BPs to inhibit calcification, hydroxyapatite breakdown and suppress bone resorption has led to the use of these substances in various clinical settings (33).

BPs have a high affinity for bone and can achieve a high concentration throughout the entire skeleton. Thus, bisphosphonates are useful for disorders which are characterized by excessive remodeling or any imbalance between osteoclast and osteoblast activities, which leads to excessive osteoclast mediated bone resorption. A temporary decrease in biochemical markers of bone resorption is seen following bisphosphonate use. Length of suppression of osteoclast function is largely a function of bisphosphonate potency for mineral matrix binding. The periods range from 1 year following oral use to up to 10 years after a single IV dose (35). There is maximum suppression of bone resorption approximately 3 months after initiation of the oral bisphosphonate therapy. Subsequently, it remains constant as the treatment continues.

Bone resorption is suppressed more rapidly after the intravenous administration as compared to oral therapy (36).

BPs are poorly absorbed from the gastrointestinal tract after oral administration. There is a less then 1% absorption from an oral dose. About 50% of the absorbed oral dose is retained in the skeleton and the remainder is excreted in the urine. The retention of bisphosphonates is primarily dependent on renal function, rate of bone turnover and binding site availability. As mentioned earlier, there is a wide variation in the amount of bisphosphonates retained after oral and IV administration (33-36). The first generation of oral BPs required patient to remain upright for 30 minutes and refrain from eating 2 hours before and at least 30 minutes after pill ingestion. The newer generation oral bisphosphonates are administered weekly (alendronate or risendronate) and monthly (ibandronate or risendronate) thus reducing the gastrointestinal symptoms and increasing patient compliance (37). BPs administered with IV (pamidronate, zoledronic acid) have further reduced the gastrointestinal effects.

BPs are widely used in a range of clinical conditions. Osteoporosis is one of the major conditions and includes osteoporosis associated with juvenile idiopathic arthritis, post- menopause, glucocorticoid use, transplants and immobility. BPs are also used in management of Paget's disease, bone malignancies, hypercalcemia and osteogenesis imperfecta (33). However, there have been multiple concerns regarding their use. Atrial fibrillation, musculoskeletal pain, hypocalcemia, acute inflammatory response, over-suppression of bone turnover, deterioration of renal function and esophageal irritation have been described. (38). Low grade fever, arthralgia's, myalgia's, headaches and flu like symptoms are seen in patients receiving oral or IV BPs (33). A further significant

concern relates to the role of BPs in the etiopathogenesis of ONJ. The relationship of BPs and ONJ is comprehensively discussed later in this review.

**2.4.2 Denosumab (Dmab):**

RANKL is produced by osteoblasts. RANKL binds to RANK (receptor activator of nuclear factor kβ) which is present on the osteoclast membrane and stimulates differentiation, activation and survival of osteoclasts. Osteoprotegerin (OPG) is a soluble RANKL-binding protein that binds with RANKL and prevents it from binding with RANK on the osteoclast membrane. Dmab is a human IgG2 monoclonal antibody, which mimics endogenous OPG which in turn prevents RANKL from binding with RANK thereby inhibiting osteoclast differentiation, activation and survival. The inhibition of osteoclast mediated resorptive activity results in an anti-resorptive effect (39,40).

Dmab is administered subcutaneously. The bioavailability of Dmab after subcutaneous injection is 61%. Its absorption is mediated by the lymphatic system. It is eliminated via the reticuloendothelial system (39).

Dmab treatment is associated with a reduction in the risk of vertebral, non-vertebral and hip fractures in post-menopausal women with osteoporosis (40). Adverse effects of Denosumab include nausea, asthenia, dyspnea, eczema and flu-like syndrome. As with the bisphosphonates, osteonecrosis of the jaw has been described as a rare but serious complication (41) (discussed later).

## 2.5 Osteomyelitis:

### 2.5.1 General considerations:

Osteomyelitis is an acute or chronic inflammatory process involving the medullary space or cortex of bone, which progresses from the initial site of involvement. The majority of osteomyelitis cases are caused by bacterial infections which results in an expanding lytic destruction of the bone with suppuration and sequestrum formation. A sequestrum represents a fragment of necrotic (non- vital) bone. The condition caused by bacterial infection is termed bacterial osteomyelitis or suppurative osteomyelitis. Acute suppurative osteomyelitis occurs when an acute inflammatory process rapidly spreads through the medullary spaces of the bone. In chronic suppurative osteomyelitis, the infected bone sequestrates and a defensive host response leads to the production of granulation tissue which subsequently forms scar tissue in an attempt to wall off the infected areas. The walled off area acts as a reservoir for bacteria, which colonizes the sequestrated bone. Antibiotics have a difficult time reaching the affected site (42). The most common cause of osteomyelitis in adults is staphylococcus aureus followed by Group A streptococcus, streptococcus pneumoniae and kingella kingae.

Acute osteomyelitis is generally seen in children due to increased vascularity in their bones and chronic osteomyelitis is seen more frequently in adults (43). Acute osteomyelitis results from bacteremic seeding of the bone due to hematogenous spread whereas chronic osteomyelitis is secondary to open fractures, soft tissue infection, bacteremic infection or infected prosthetic joints (43). Patients with underlying medical conditions such as diabetes mellitus, anemia, malnutrition, chronic renal disease and cancer are more prone to chronic osteomyelitis. Soft tissue injury and lack of peripheral

vascularization in diabetic patients, may reduce awareness of wounds and cause increased risk of infections (44). There have been multiple classifications of osteomyelitis in the long bones. A common classification of long bone osteomyelitis is the Cierny-Mader classification shown below which is based on the anatomy of the bone infection and physiology of the host.

Cierny- Mader classification:

| | |
|---|---|
| Anatomic Type | Stage 1: Medullary osteomyelitis |
| | Stage 2: Superficial osteomyelitis |
| | Stage 3: Localized osteomyelitis |
| | Stage 4: Diffuse osteomyelitis |
| Physiologic Type | A Host: Normal Host |
| | B Host: Systemic compromise (Bs) |
| | Local compromise (Bl) |
| | C Host: Treatment worse than the disease |

The clinical symptoms of osteomyelitis are variable based on acute or chronic presentation. Acute osteomyelitis is characterized by pain, swelling, muscle tenderness and muscle wasting. Chronic osteomyelitis is characterized by pain, limited mobility, redness, swelling and persistent sinus tract or wound drainage, poor wound healing fever and malaise (43). The recurrence rate of chronic osteomyelitis in adults is about 30% at 12 months (45). The incidence has drastically decreased since the introduction of antibiotics (46).

### 2.5.2 Osteomyelitis of the jawbones:

The jaws have anatomically unique features which distinguish these bones from other parts of the skeleton. These include the periodontal adaptions to support teeth, the chronic exposure to the oral microbial microenvironment through periodontal attachment junctions and coverage with both skin and mucosal layers. The mucosal coverage is associated with the potential for constitutive exposure to oral secretions and a range of microbes in the event of any form of barrier disruption. Lastly, there are the stressful functional requirements related to the multi-directional impacts associated with mastication. The specific local anatomic, functional, immunological and microbiological considerations impact the etiopathogenesis and treatment of osteomyelitis involving jaw bones. Thus, it is not surprising that there are differences from osteomyelitis of the long bones, which are reflected in a more complex classification.

Different classifications have been proposed based on clinical course, anatomic-pathological considerations, radiological features, etiology and pathogenesis. The classification of the osteomyelitis of the jaw bones can be confusing due to wide variety of terms used to describe the same disease. In table 1, below two different classifications have been shown with their criteria. Both the classifications are based on clinical, radiological and etiological factors.

Table 1: Classification of Osteomyelitis of the Jaw

| Reference | Classification | Classification criteria |
|---|---|---|
| Marx RE<br>Chronic Osteomyelitis of the Jaws<br>Oral and Maxillofacial Surgery Clinics<br>of North America, Vol 3, No 2, May 91,<br>367-81.<br><br>Mercuri LG<br>Acute Osteomyelitis of the Jaws<br>Oral and Maxillofacial Surgery Clinics<br>of North America, Vol 3, No 2, May 91,<br>355-65 | I**. Acute osteomyelitis**<br>1. Associated with Hematogenous spread*<br>2. Associated with intrinsic bone<br>pathology or peripheral vascular<br>disease*<br>3. Associated with odontogenic and nonodontogenic local processes*<br>**II. Chronic osteomyelitis**<br>1. Chronic recurrent multifocal osteomyelitis of children<br>2. Garrè's osteomyelitis<br>3. Chronic suppurative osteomyelitis<br>– Foreign body related<br>– Systemic disease related<br>– Related to persistent or resistant organisms<br>4. True chronic di | Classification based on clinical picture and radiology, etiology, and pathophysiology<br>Classification of acute osteomyelitis by Mercuri, classification of chronic osteomyelitis by Marx. The arbitrary time limit of one month is used to differ<br>acute from chronic osteomyelitis<br>* From Waldvogel and Medo# 1970 |
| Topazian RG<br>Osteomyelitis of the Jaws. In Topizan RG, Goldberg MH (eds): Oral and Maxillofacial Infections.<br>Philadelphia, WB Saunders 1994,<br>Chapter 7, pp 251-88 | I. Suppurative osteomyelitis<br>1. Acute suppurative osteomyelitis<br>2. Chronic suppurative osteomyelitis<br>– Primary chronic suppurative osteomyelitis<br>– Secondary chronic suppurative osteomyelitis<br>3. Infantile osteomyelitis<br>II. Nonsuppurative osteomyelitis<br>1. Chronic sclerosing osteomyelitis | Classification based on clinical picture,<br>radiology, and etiology (specific forms such as syphilitic,<br>tuberculous, brucellar, viral, chemical, Escherichia coli and Salmonella osteomyelitis not integrated in classification) |

| | | |
|---|---|---|
| | – Focal sclerosing osteomyelitis<br>– Di#use sclerosing osteomyelitis<br>2. Garrè's sclerosing osteomyelitis<br>3. Actinomycotic osteomyelitis<br>4. Radiation osteomyelitis and necrosis | |

OM diagnosis includes laboratory testing and radiological findings. Laboratory testing shows elevated peripheral white blood cells, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Blood culture may be positive (43).

Plain radiography, bone scintigraphy, computed tomography(CT) and magnetic resonance imaging (MRI) are useful for the diagnosis of osteomyelitis (47). Plain radiography does not reveal abnormalities of the bone until at least 2 weeks of its initiation. MRI and bone scintigraphy are more commonly used and are more accurate imaging modalities for the diagnosis of the osteomyelitis. These are able to identify the changes in the bone within a few days of initiation. The sensitivity of MRI and bone scintigraphy is comparable but specificity of the bone scintigraphy is low if the patient has had recent surgery or trauma (43,48,49, 50,51).

Treatment of osteomyelitis is similar to long bones. It involves appropriate antibiotic therapy and possible surgical removal of infected and necrotic tissues and possible infected surgical hardware. Choice of antibiotic therapy is determined by culture and susceptibility (52,53,54).

## 2.6 Osteonecrosis:

### 2.6.1 General considerations:

The National Institute of Arthritis and Musculoskeletal and Skin Diseases defines osteonecrosis (ON) as a disease in which a temporary or permanent loss of the blood supply to the bone causes bone tissue to die and the bone to collapse. It is also known as avascular necrosis, aseptic necrosis or ischemic necrosis. Thus, a key distinction from the necrotic bone, which develops in osteomyelitis is the absence of an infective component (55).

Osteonecrosis can occur at any age but is generally seen in the $4^{th}$ to $6^{th}$ decades of life. It mainly affects the long bone epiphyses, femoral and humeral heads and distal ends of the tibia. It often shows a multifocal distribution. Osteonecrosis can occur due to various underlying causes; these are discussed in the next section (55).

### 2.6.2 Pathogenesis:

Osteonecrosis is multifactorial and can be caused by various mechanisms involving compromised circulation or disruption of blood supply. The bone ischemia causes an inflammatory response which results in resorption of the bone. There are two pathogenic pathways: traumatic or atraumatic. As the name suggests, the traumatic pathway is due to an injury resulting in disruption of blood flow. The atraumatic pathway is caused by decreased blood flow due to alcohol, drugs, toxins, radiation, sickle cell crisis, developmental vascular problems, athero-sclerotic disease resulting in coagulopathy and Gaucher's disease. Other predisposing factors include steroid medications, systemic lupus erythematosus, thrombophilia, HIV infection, pancreatitis

and alcohol use. A history of radiation treatment, chemotherapy and organ transplants and immunosuppressive conditions are further known risk factors (55,56,57).

Osteonecrosis is associated with a complex process of bone resorption and formation. The initial step of osteonecrosis is the necrosis of hematopoietic cells and adipocytes followed by interstitial marrow edema (58). The initial changes are characterized by osteocyte necrosis as indicated initially by development of pyknotic nuclei. This is typically followed by cell necrosis, which results in empty osteocyte lacunae (58). Reactive hyperemia and capillary revascularization initiates a process of bone resorption and production that incompletely replaces dead with living bone (59). There is evidence suggesting that the pathophysiology of osteonecrosis in this site involves compromised microcirculation due to vascular interruption, intravascular occlusion and extravascular compression (59). Intraosseous hypertension has also been recently associated with osteonecrosis (60). These studies have led to the suggestion that elevated intraosseous pressure is a non- specific factor in the pathogenesis of osteonecrosis, presumably by compromising the circulation.

**2.6.3 Osteonecrosis of the long bones:**

Hip and knee joints are the sites most commonly affected by osteonecrosis. Bone infarcts are commonly seen adjacent to the joints associated with the femoral head, humeral head, knee, small bones of the hand and foot and the vertebrae. Osteonecrosis of the knee was initially described as a distinct entity in1968. It is often seen in elderly women with a previous history of osteoporosis. There may not be an associated history of systemic diseases (61). The majority of the femoral head avascular necrosis conditions

are idiopathic although there is often a history of these patients being treated with corticosteroids or are alcoholics.

ON is typically seen in the cortical surface of the long bones. This is due to a predisposition related to lack of collateral circulation and smaller diameter of the blood vessels.

Conservative management strategies of ON include hyperbaric oxygen, pulsed electromagnetic therapy and extracorporeal shockwave therapy. Pharmacologic management of osteonecrosis has involved use of BPs, prostaglandin, enoxaparin and statins. BPs are used in management of ON in long bones and counterintuitively have been implicated with causation of ON in jaw bones. This is explained by the distinctive pathogenic mechanisms of ON in long bones. The ON in long bones is caused by disruption of blood supply as a result of subchondral trabecular fracture which is prevented by BPs. (62,63,64).

Enoxaparin, low molecular weight heparin, has been used to prevent progression of ON by improving blood circulation.

Iloprost is a vasoactive synthetic prostacyclin analog. It functions to dilate arterial and venous vascular beds, reduce capillary permeability and inhibit platelet aggregation (65).

Statins are used for the treatment of ON by increasing expression of BMP-2 and decreasing expression of the adipocyte gene, resulting in a reduction in intraosseous pressure (66,67).

### 2.6.4 Osteonecrosis of the jaw:

Osteonecrosis of the jaw (ONJ) is seen as a complication in patients being treated with bisphosphonate medications or following radiotherapy for head and neck carcinoma (osteoradionecrosis) (61). The majority of the cases not associated with radiotherapy have been documented in patients who were treated with bisphosphonates. 95% of these patients were being treated with high dose intravenous bisphosphonates as part of the management of malignancies such as multiple myeloma and metastatic bone cancers. The remaining 5% of these cases were reported in patients receiving low dose bisphosphonate therapy (35). Thus, the diagnosis of ONJ has usually been assumed to be associated with use of anti-resorptive medications unless otherwise stated.

The American Society for Bone and Mineral Research (ASBMR) defines medication related osteonecrosis of the jaw (MRONJ) as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a BP and who has not received radiation therapy to the craniofacial region. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has recently (2014) updated their MRONJ definition as follows:

1. Current or previous treatment with anti-resorptive or antiangiogenic agents;
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks; and
3. No history of radiation therapy to the jaws or obvious metastatic disease to

the jaws.

The differential diagnosis of MRONJ include periapical pathosis, gingivitis, periodontal disease, mucositis, infectious osteomyelitis, osteoradionecrosis and neuralgia inducing cavitation osteonecrosis (a controversial concept). It can also be confused with other common oral conditions such as alveolar osteitis, fibro-osseous lesions, sarcomas, chronic sclerosing osteomyelitis and temporomandibular joint disease (4).

Patient history and clinical examination are important in the diagnosis of ONJ. Patients with mild to moderate disease require minimally invasive treatment involving pain and infection control. Patients with advanced disease may benefit from surgical treatment.

Staging of ONJ is important for diagnosis and treatment. The AAOMS has proposed staging which relies on clinical and radiographic examinations. This is shown in the following table:

Table 2: Staging and treatment strategies of MRONJ

| **MRONJ Staging** | **Treatment Strategies** |
|---|---|
| **At risk category** No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates | • No treatment indicated<br>• Patient education |
| **Stage 0** No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms | • Systemic management, including the use of pain medication and antibiotics |
| **Stage 1** Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection | • Antibacterial mouth rinse<br>• Clinical follow-up on a quarterly basis<br>• Patient education and review of indications for continued bisphosphonate therapy |
| **Stage 2** Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage | • Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse<br>• Pain control<br>• Debridement to relieve soft tissue irritation and infection control |
| **Stage 3** Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor . | • Antibacterial mouth rinse<br>• Antibiotic therapy and pain control<br>• Surgical debridement/resection for longer term palliation of infection and pain |

Multiple hypotheses have been advanced to explain the pathophysiology of osteonecrosis. These multiple hypotheses are not exclusionary. These include the following (3,4):

1. Bone remodeling inhibition- Osteoclast activity is constantly regulated by RANKL and OPG signaling. Bisphosphonates have direct inhibitory effect on osteoclasts causing significant decrease in bone remodeling. Since the alveolar bone of the jaw has an increased rate of remodeling, compared to other bones in the skeleton, the jaw bones would be disproportionately affected by the bisphosphonates.
2. Inflammation and infection: In patients with ongoing bisphosphonate therapy, tooth extraction is the most common ONJ inciting event and bone exposure in this area is much more common than other anatomic sites. Histopathological evaluation of the necrotic bone from these sites reveals association with bacterial and fungal infection.
3. Inhibition of angiogenesis: Necrosis of the bones occurs due to decrease in vascular supply. Antiangiogenic medications are utilized to inhibit tumor invasion and metastasis targeting vascular endothelial growth factors (VEGF). Bisphosphonates have anti-angiogenic properties.
4. Direct soft tissue toxicity: Although BPs target the osteoclasts and bind to hydroxyapatite in bone, soft tissue toxicities have been reported. Multiple cell types such as cervical, prostate and oral epithelial cells have exhibited increased apoptosis or decreased proliferation after exposure to BPs.

**2.6.4.1 Risk of MRONJ in osteoporosis patients:**

Prevalence:

Studies have shown highly variable results This is probably related to inadequacies in the study design and lack of rigor in methodology. Prevalence of ONJ in patients administered oral BPs for osteoporosis varies from 0-0.04%, with the majority being below 0.001%(5,68-77). Another study indicated prevalence of MRONJ in patients receiving long term bisphosphonate therapy was 0.1% which increased to 0.21% among those patients who have taken oral BP greater than 4 years (73). The median duration of exposure was 4.4 years at the time of development of ONJ and ONJ like features.

Prevalence of ONJ in patients treated for osteoporosis with IV BPs is much higher than that's seen in patients treated with oral bisphosphonates. The prevalence rates vary from 0% to 0.348% and majority of the studies show results below 0.005%(68,69,78,79,80). Khan et al reported a prevalence of ONJ in patients on BP to be approximately 0.001%. Felsneberg reported a prevalence <1/100,000 population who were on BPS (81,82). Papolous et al showed that patients on Denosumab have 0.04%(4 per 10,000 cases) risk of MRONJ (83).

Incidence:

Incidence of ONJ in patients prescribed oral BP is 1.04-69 per 100,000 (0.001%-0.064%) patients per year (82,84,85). Incidence of ONJ in patients prescribed IV BPs varies from 0-90 per 100,000 patients per year (78,79,85,86). Incidence of patients who are treated with Dmab varies from 0-30.2 per 100,000 patients per year (83,87,88). Ulmner and colleagues surveyed oral surgeons and dental clinics to find an incidence

rate of 0.067%(89). Mavrokokki et al found the incidence rate of ONJ to be 0.01% -0.04% in osteoporotic patients receiving BP nationwide (75). Patients exposed to zolendronate therapy once a year for 3 years reported are at risk of MRONJ of 0.017%(1.7 cases per 10,000 patients). These patients were followed for 6 years which did not show any increase in the incidence (90). Comparison between patients exposed to Denosumab for osteoporosis was 0.04% (4 out of 10,000 patients) and patients exposed to placebo medication was 0.02% (2 cases per 10,000 patients) (83,90). Based on the studies mentioned above the risk of ONJ in osteoporotic patients treated with oral or IV BPs or Dmab is very low.

**2.6.4.2 Risk of MRONJ in cancer patients:**

Risk of ONJ in cancer patients is much higher than in patients treated for osteoporosis.

Prevalence:

Prevalence of MRONJ in cancer patients ranges from 0%-0.186% (186 per 10,000 patients) (68,91-115).

Incidence:

The incidence of MRONJ in patients treated with cancer may vary with types of cancers. Other variables such as anti-angiogenic drugs and glucocorticoids also affect the incidence rates in these patients. Multiple studies show the incidence of MRONJ in patients treated for malignancy with BPs is very high ranging 0 to 12,222 per 100,000 patients per year (82,85,116-157). Incidence of MRONJ in patients treated for malignancy with denosumab was from 0 to 2316 per 100,000 patients-year (129,132,145,149-151,158).

Incidence of MRONJ in patients exposed to zolendronate ranges from 0.7% to 6.7%(123,159). Whereas in patients treated with Denosumab the risk of MRONJ ranges from 0.7% to 1.9% (70-90 cases per 10,000 patients) (145,160).

A wide variation is seen in the incidence and prevalence of these multiple studies due to the use of different medications, protocols and the type of malignancy. Epidemiological data on the prevalence and incidence of ONJ are limited and, when available, typically not based on prospective studies or population-based surveys.

**A. Duration of Medication Therapy as a Risk Factor for MRONJ:**

Duration of therapy is another important confounding variable for the development of MRONJ in patients treated with anti angiogenic or anti resorptive medications. The duration of the treatment with the medication is directly proportional to the increased risk of development of MRONJ in these patients. In the Henry et al's study, a randomized double blinded study, of Denosumab vs zolendronic acid, the incidence of developing ONJ was 0.5 or 0.6% at 1 year, 0.95% or 1.1% at 2 years and1.3% or 1.1% at 3 years. The risk of MRONJ in Denosumab exposed patients plateaued between 2 and 3 years (132). In another study, the investigators combined 3 blinded phase 3 trials and found similar results for patients treated with Denosumab (10).

**B Local factors:**

1. Dento-alveolar Surgery:

Extractions are considered as a major risk factor. The estimated risk of MRONJ in patients treated with oral BPs after tooth extraction is 0.5%(161). This was derived from evaluation of 194 patients exposed to oral BP who underwent extraction of at least one

tooth. 52% to 61% of patients have reported tooth extraction as a predisposing event (10,159,162).

In a longitudinal cohort study by Vahtesavnos et al, patients treated with IV BPs (zoledronate), tooth extraction was associated with 33 times increased risk of ONJ (159). Another case control study of patients with cancer exposed to zolendronate, tooth extraction was reported to be associated with 16 times increased risk of ONJ (163).

Risk of developing MRONJ in patients exposed to IV bisphosphonates varies from 1.6% to 14.8% (AAOMS position paper). In two of the prospective cohort studies each with 176 and 63 cancer patients exposed to zolendronate and IV BPs 5(2.8%) and 1(1.6%) developed ONJ (164,165). The risk of MRONJ in patients who are exposed to IV BPs ranges from 1.6% to 14.8% (77). The risk of MRONJ in patients who are treated for periodontal disease or endodontic procedures and dental implants is unknown.

2. Anatomic Factors:

There is an increased prevalence of MRONJ in the mandible (73%) as compared to the maxilla (25%) (10).

**C. Systemic and Other Medication Factors:**

Corticosteroids are associated with increased risk of MRONJ. Patients taking anti resorptive medications in association with anti angiogenic medications are at a greater risk of MRONJ (10,166). Anemia, diabetes and type of cancer are associated comorbid conditions associated with an increased risk of MRONJ (10).

**D. Demographics:**

There have been multiple studies that have assessed age and gender incidence for MRONJ patients. There is a higher prevalence in females than males. The higher prevalence in females can be explained as a result of the greater female association with diseases, such as osteoporosis and breast cancer, which have been managed with bisphosphonates (10,90). There is very limited data on MRONJ incidence in pediatric population.

**2.7 Oral ulceration with bone sequestration:**

Oral ulceration with bone sequestration represents a mucosal ulcer with an exposed necrotic bone base (20). The condition was initially described as “lingual mandibular sequestration and ulceration” by Peters et al in 1993. Subsequent similar reports suggested the condition be renamed as “spontaneous sequestration of the lingual mandible bone” in the area of mylohyoid ridge (2,167). The current most accepted term is “oral ulceration with bone sequestration(OUBS)” (20).

**2.7.1 Pathogenesis:**

Pathogenesis of OUBS is not well understood. It has been hypothesized that it begins as a traumatic ulcer (11,12,18,168). Bone sequestration could occur due to disruption of blood supply from the periosteal layer to the poorly vascularized superficial cortical bone and possible secondary infection. A link between oral ulceration and bacterial colonization has also been described in Farah and Savage’s study in 2003(168). According to them, the posterior mandible harbors more bacteria due to relative inflexibility of the posterior tongue and overload of masticatory forces which renders the

area more susceptible to trauma. Many histologic reports have shown a heavy bacterial colonization of the sequestrum.

There are multiple anatomic factors that also predispose patients to the OUBS condition. The mylohyoid ridge, mandibular tori and maxillary tori are the most prevalent areas in a decreasing order (168). These areas are more prone to trauma and necrosis due to their thin mucosal lining and poor vascular supply. Chanavaz et al hypothesized that lack of fibrous connective tissue in these areas predisposed them to acute or chronic trauma and the decreased vascular supply leads to decreased capacity to resist infections (169).

Other authors have generalized the OUBS concept, recognizing the predisposing influence of a variety of well-known systemic factors (2,167). In addition to the anti-resorptive medications, these include a broad list of factors including systemic medications (systemic corticosteroids, other immunomodulatory drugs), infections (bacterial, viral, fungal and parasitic), trauma (masticatory or factitial) and other disorders (neoplasia, bone disorders, congenital defects and immunologic defects). Another case series published in 2017 described the use of methotrexate for arthritis in 3 of 6 cases. Other systemic medications in the same case series were etanercept, prednisone, adalimumab and rituximab. These observations are consistent with the OUBS concept.

In summary, the ulcers with subjacent sequestrations can occur in healthy patients in anatomically predisposed sites but would obviously be more likely and show greater morbidity if there was a superimposed predilection (170).

### 2.7.2 OUBS literature search:

A total of 19 case reports or case series describing 44 cases were found in a search of the OUBS literature (11-18, 23,167,171-178). The reports are indicated in Table 3 below.

Table 3: Parameters from OUBS case reports

| Study | Case # | Age | Sex | Anatomical location | Clinical presentation and duration |
|---|---|---|---|---|---|
| Peters et al 1993 | 1 | 53 | Female | Lingual mucosa covering mylohyoid ridge | 3mm ulcer with 2 mm sequestrum symptomatic 12 weeks |
| | 2 | 55 | Male | Lingual mucosa covering mylohyoid ridge | 3mm ulcer with 3mm sequestrum symptomatic 8 weeks |
| | 3 | 42 | Female | Lingual mucosa covering mylohyoid ridge | 3mm sequestrum symptomatic 3 weeks |
| | 4 | 32 | Male | Lingual mucosa covering mylohyoid ridge | 3-4mm ulcer with 4mm sequestrum ,symptomatic few months |
| | 5 | 50 | Female | Lingual mucosa covering mylohyoid ridge | 4mm sequestrum |
| | 6 | 34 | Male | Lingual mucosa covering mylohyoid ridge | 3mm sequestrum symptomatic 2 weeks |

| | | | | | |
|---|---|---|---|---|---|
| | 7 | 33 | Male | Lingual mucosa covering mylohyoid ridge | 8mm ulcer with 6mm sequestrum symptomatic 1 week |
| | 8 | 47 | Male | Lingual mucosa covering mylohyoid ridge | 6mm sequestrum |
| | 9 | 57 | Male | Lingual mucosa covering mylohyoid ridge | 3mm ulcer with 2 mm sequestrum symptomatic 3 weeks |
| | 10 | 55 | Female | Lingual mucosa covering mylohyoid ridge | 4mmulcer with 10mm sequestrum |
| | 11 | 40 | Male | Lingual mucosa covering mylohyoid ridge | 8mm ulcer with 3 mm sequestrum |
| Sonnier and Horning 1997 | 1 | 32 | Male | Left lingual mucosa near tooth #34 | Ulceration with 3 bony lesions on central tori symptomatic 4 months. |
| | 2 | 53 | Male | Bilateral mandibular lingual mucosa | 10mm ulcers bilaterally with necrotic bone sequestrum, symptomatic 2 weeks. |
| | 3 | 38 | Female | Right lingual mucosa on mandibular near teeth #45 and #46 | No ulceration ,3 sinus tracts leading to multiple bony lesions (5x15x1mm) on exostoses; symptomatic 2 weeks. |
| | 4 | 33 | Male | Biopsy on facial gingiva near teeth #15 and #16; sequestrum near tooth #28; sequestrum near sinus tract of tooth #26. | No ulceration, 1 sinus tract 3x2x1mm sequestrum; symptomatic 1 month. |
| Flaitz 2000 | 1 | 56 | Female | Left lingual mucosa covering mylohyoid ridge near left molars | Ulcer (3x8mm) with exposed necrotic bone sequestrum. |

| | | | | | |
|---|---|---|---|---|---|
| Scully 2002 | 1 | 45 | Male | Inferior to left mandibular oblique ridge | 5mm ulcer with 3 mm sequestrum symptomatic 5 days |
| | 2 | 53 | Male | Inferior to left mandibular oblique ridge | 5mm ulcer with 4mm sequestrum symptomatic 10 days |
| Friel and Macintyre 2002 | 1 | 64 | Female | Right mylohyoid ridge | <1cm in size for the ulcer and Unknown duration |
| Peters et al 2003 | 1 | 55 | Male | Left mylohyoid ridge | Ulceration |
| Kessler 2005 | 1 | 40 | Male | Right lingual mucosa covering mylohyoid ridge near molar region | Ulceration and exposed necrotic bone sequestrum ; symptomatic 3 weeks. |
| Carrard et al 2009 | 1 | 38 | Male | Bilateral exostoses in mandibular lingual molar area | Bilateral ulcerations (15x7mm) with exposed necrotic bone sequestrum; symptomatic 1 month. |
| Jackson and Malden 2007 | 1 | 41 | Male | Right lingual mucosa covering mylohyoid ridge near molars | 12mm ulceration and exposed necrotic bone sequestrum; symptomatic 2 months. |
| | 2 | 57 | Male | Right lingual mucosa covering mylohyoid ridge and molar region. | 15mm ulceration and exposed necrotic bone sequestrum; symptomatic 1 week. |
| | 3 | 48 | Male | Left lingual mucosa covering mylohyoid ridge near molar region. | 12mm ulceration and exposed necrotic bone sequestrum; symptomatic 2 months. |
| Gunduz et al 2009 | 1 | 44 | Male | Right lingual mucosa | 5mm ulceration 7 days was surgically removed. |
| Almarazoo et al 2010 | 1 | 60 | Male | Right mylohyoid ridge | Ulcer healed in 1 month |

| | | | | | |
|---|---|---|---|---|---|
| | 2 | 67 | Female | Right torus mandibularis | Ulcer<br><br>>1month,soreness,pain |
| Koshal et al 2010 | 1 | 5 | Male | Left mandibular buccal alveolus with deciduous canine and first molar (#73 &#74). | Demarcated necrotic non healing alveolar bone division. |
| Villa and Gohel 2014 | 1 | 45 | Female | Right mylohyoid ridge | Painful ulcer 21 days |
| Kharazmi et al 2015 | 1 | 69 | male | Right mylohyoid ridge | Painful ulcer 14 days |
| | | 86 | male | Right mylohyoid ridge | Painful ulcer 14 days |
| Alkhabuli et al 2017 | 1 | 49 | Male | Right mylohyoid ridge | Ulcer 3 days |
| Kharazmi et al 2017 | 1 | 41 | Female | Right mylohyoid ridge | Ulcer healed in 22 days |
| Gabric et al 2017 | 1 | 38 | Female | Left mylohyoid ridge | Unknown |
| Cerruto et al 2018 | 1 | 43 | Male | Right mylohyoid ridge | Pain burning sensation 2 days |
| Thermos et al 2018 | 1 | 58 | Male | Palatal exostoses near the upper left second molar | Pain, 15 days |
| | 2 | 75 | Female | Labial mandibular exostosis near the | 1 year |
| | 3 | 54 | Male | Mylohyoid ridge near first molar | Pain ,5 days |
| | 4 | 27 | Male | Maxillary buccal exostoses near $1^{st}$premolar | Unknown |
| | 5 | 40 | Male | Mylohyoid ridge near left second premolar | Pain and ulceration 30 days |
| | 6 | 47 | Female | Maxillary exostoses above right first premolar | Unknown, 1 year |

| | | | | | |
|---|---|---|---|---|---|
| | 7 | 36 | Male | Mylohyoid ridge near left 1 st molar | Painful ulcer 25 days |
| | 8 | 43 | Female | Mylohyoid ridge | Pain, swelling, 14 days |

Summations from the above table indicate, there is a predilection for middle age (47.2 years, SD=12.0) with only 1 case occurring in a child (5 years). There were 30 males and 14 females suggesting a male gender predilection. On a speculative note, possibly, male gender might be associated with OUBS because of increased alcohol consumption, tobacco use, increased masticatory loads and prominent mylohyoid ridge. The healing time of these patients varied from 1 week to 16 weeks with 12 cases healing within 8 weeks. In the 40 cases where duration was documented 7 lasted for more than 8 weeks. 37 of the 44 cases were on the lingual mandibular mucosa with majority at the level of the mylohyoid ridge. 6 cases were reported to be involving exostoses.

## 3. Materials and Methods

Research ethics approval for this project was obtained from University of Alberta Health Sciences Research Ethics Board- Health Panel (HREB).

### 3.1 Preliminary study

In view of suggestions that the OUBS condition was extremely rare, a preliminary study was done to try to assess how often these cases were submitted for histopathologic review as a proportion of all the cases involving a non-vital bone biopsy. This was done with a retrospective review of cases of jaw sequestration submitted over a 3-year period (1988-1990), before the use of anti-resorptive medications, from the Oral Pathology archives at University of Alberta. The methods and results of this investigation are indicated in Appendix 1. A subset of cases which matched the OUBS profile were separated. From these, a further group of cases were separated in which the exposed bone had been present for more than 8 weeks. Fourteen of 48 cases (29%) matched the OUBS profile. Of further interest, 3 cases (6%) had persisted beyond 8 weeks which also matched the MRONJ profile. These findings suggested that the OUBS presentation was not uncommon and that it occurred with a frequency which was comparable to other conditions resulting in necrotic bone. Thus, a survey study appeared to be feasible.

### 3.2 Survey study:

The study was a clinical non-interventional cross-sectional survey study. The target audience was the total population of primary care general dental practioners (GDP) in Alberta.

A one-page information sheet was designed to be read by the respondent before completing the survey. The information sheet included a brief description of the anti-resorptive medications, a case definition of MRONJ and a brief description of OUBS, which needed to be distinguished from MRONJ (Appendix 2).

The survey form (Appendix 3) attempted to elicit information regarding the following:

- Number of years the GDP has been engaged in clinical practice.
- Average number of patients in their care.
- Information regarding OUBS cases seen ever and/or in the past 2 years.
- Site/location of the OUBS.
- Management of the identified cases.
- The elapsed time before resolution.
- Information regarding MRONJ cases seen in the practice.

The aim was to assess the OUBS incidence as extrapolated from the estimated number of patients in the care of respondents.

OUBS inclusion criteria were as follows:

- Cases meeting the OUBS case definition.
- Reliable clinical information regarding the presenting patient

OUBS exclusion criteria:

- Any prior or current use of anti-resorptive medication.

The survey form was initially tested on a GDP focus group, which resulted in 3 modifications of the survey process. The first was the recognition that to obtain an accurate report, each respondent needed to undergo a brief clinical informational session or a tutorial before being asked to indicate their memory of clinical observations. The second was that an inducement should be offered to improve response rate. The third was that a one- page survey instrument was more likely to be completed than a longer survey.

Two strategies were used to access Albertan GDPs and invite them to participate in the survey. The first was through the participation of various non-selected groups of GDPs in Continuing Dental Education courses at the University of Alberta. The second was through a WEB-based survey; the latter approach accessed every GDP in Alberta. Correspondingly, the informational sessions which preceded completion of the survey form were presented in two formats. The first was a brief 5-minute tutorial, which was designed to be presented before the survey was distributed to the groups participating in continuing education courses (Appendix 4a). After presenting the tutorial, the GDPs were provided with the information sheet and survey sheet to complete the survey. The second information initiative was designed to be used for those respondents who were accessed through a WEB based survey. In these cases, the tutorial involved a case challenge regarding OUBS, which was published in the Alberta Dental Association and College (ADA&C) provincial newsletter, the ADA&C Updater. (Appendix 4b). The case challenge was followed by an invitation to access an on-line survey which was posted on the School of Dentistry, University of Alberta website. The website also included a copy of the case

challenge that was published in the Updater. The respondents could return the completed form via e mail or fax.

With both survey approaches, the survey invitation included an inducement in the form of a discount on future dental continuing education courses at the School of Dentistry, University of Alberta. Reminders were published in two subsequent editions of the ADA&C Updater.

The informational sessions (tutorial and case challenge) showed clinical images of the OUBS condition and indicated the clinical presenting criteria. Fig.1, 2,3 and 4 show representative clinical, radiologic and histopathologic images of the condition.

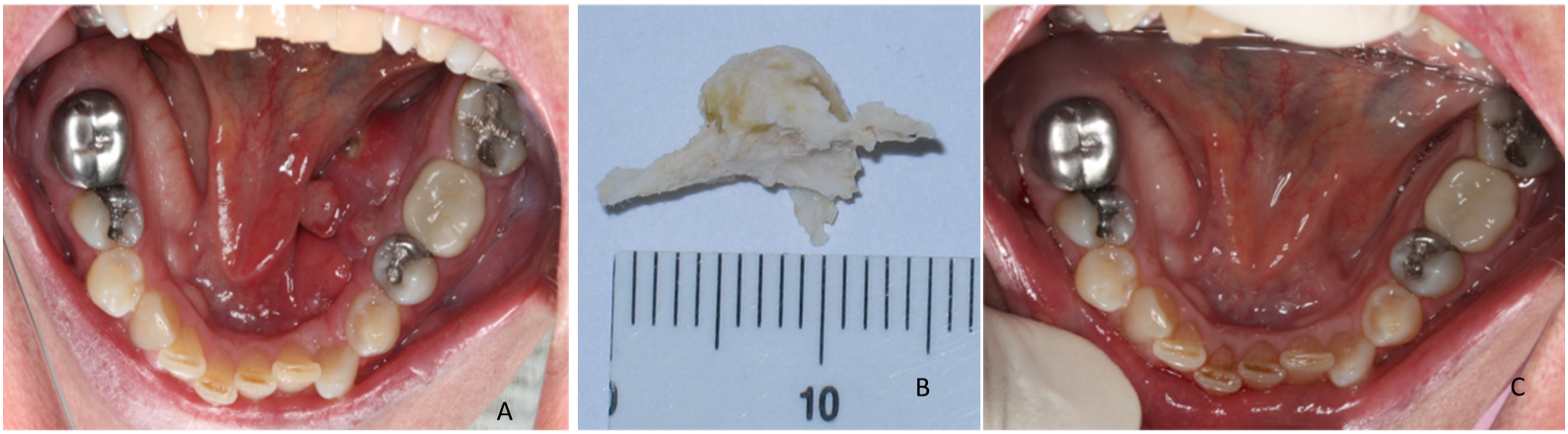



Fig. 1: 64 year old healthy woman with painful exposed bone associated with the left mandibular torus for over 2 months (A). Medications: Adalat. At exam, a large bone fragment had spontaneously extruded (B) and the lesion was resolving. Two months later, there was a second spontaneous sequestration involving the right torus, which also resolved. Fig 1C shows healing after 5 months. After 5 year, there have been no further recurrences.

*Acknowledgement: Clinical photos contributed by Dr. Jack Quon*.

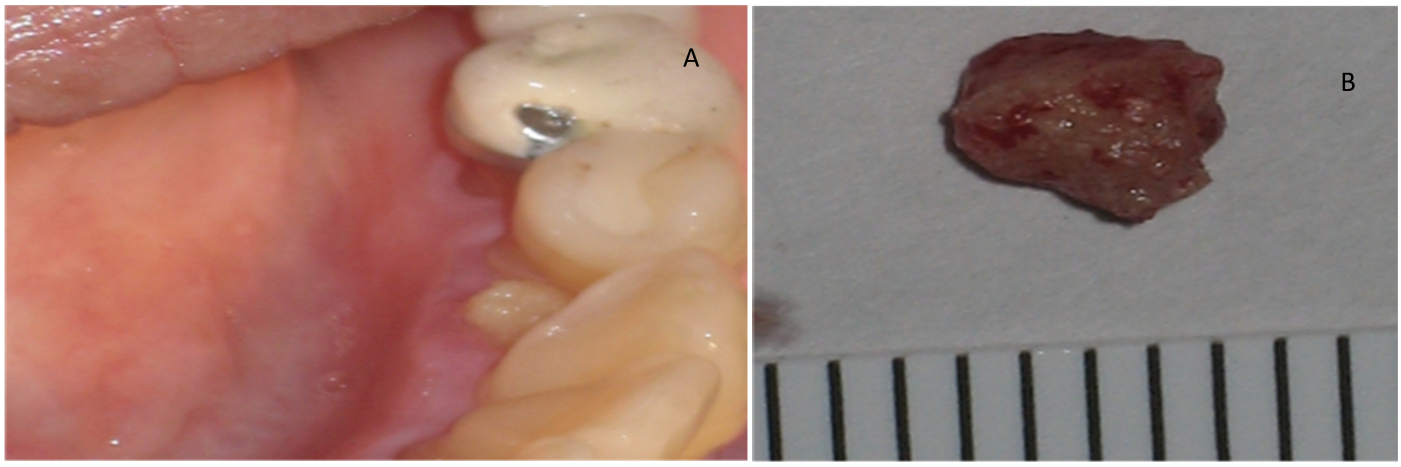



Figure 2: 44 year old healthy woman with asymptomatic exposed bone for over 3 months (A). Medications: None. Bone fragment (B) removed under local anesthesia. No recurrence after 6 months.

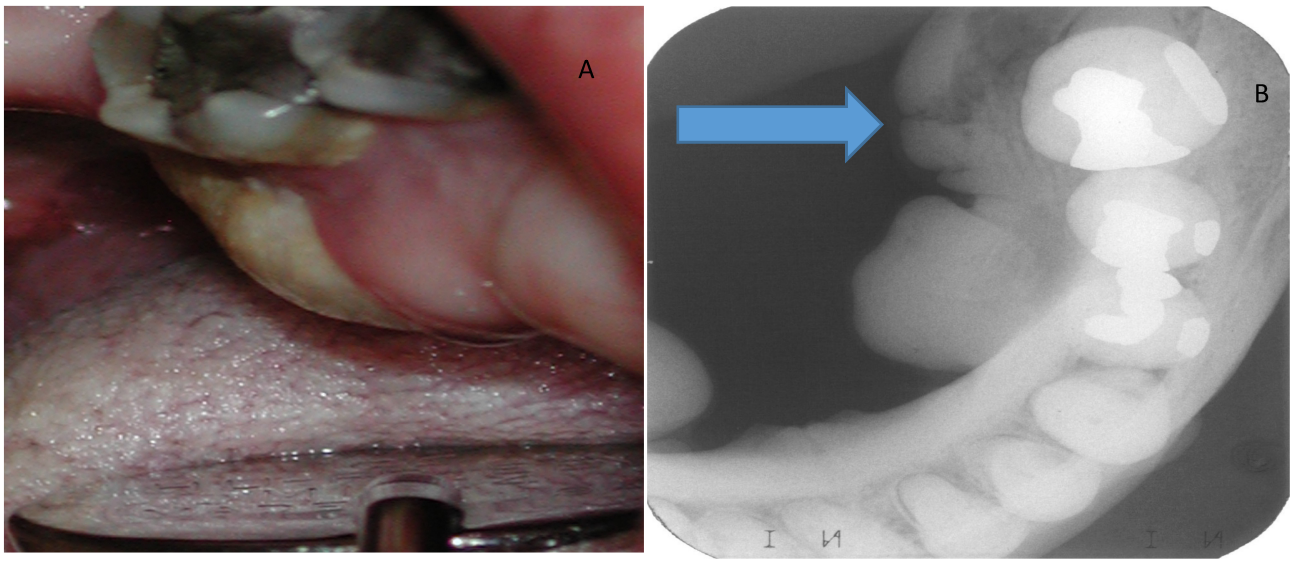



Fig 3: The clinical picture(A) shows a large ulcer with a necrotic bone base involving the left lingual mandible. The occlusal radiograph(B) shows the sequestrating bone. The peripheral sequestration is best imaged with an occlusal radiograph and is usually not visible on a periapical film.

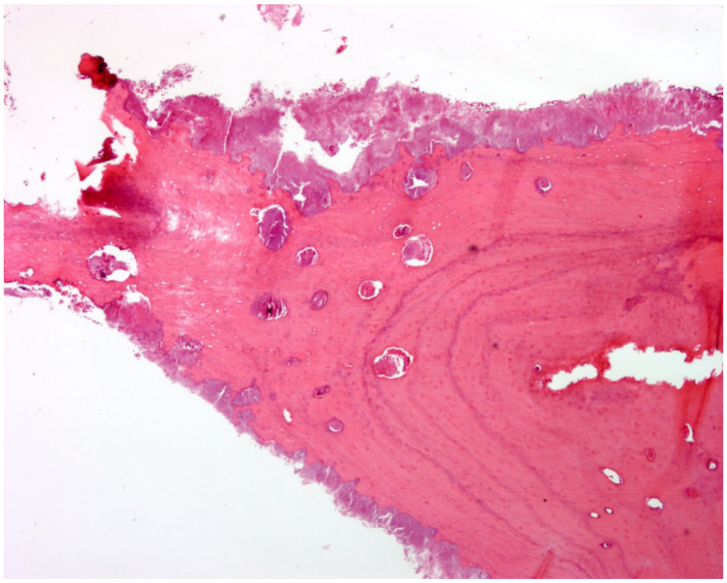


Fig. 4: Histopathological presentation of a bone sequestrum from an OUBS case. Peripherally there is irregular resorption and extensive colonization with non-specific microbial masses.

With both survey approaches, to minimize notoriety bias, respondents were specifically requested to respond in the event they had never seen any OUBS cases.

The completed survey questionnaires were collected personally by the principal investigator.

**3.3 Statistical analysis:**

The completed surveys were numbered and the data was anonymously entered into an Excel spread sheet under the previously noted data categories. Descriptive statistics were used to analyze the data. No pre-existing data was available for comparative purposes.

## 4. Results

391 responses were collected representing a 95% confidence level (5% confidence interval). This number reflects 20% of all the GDPs in the province.

The mean practice size was 1750 patients (SD = 105). This translates into informed observations by GDPs of a population of 685,000 patients, which is about 17% of the current Alberta population.

Overall, 51 GDPs (13 % of respondents) had seen the OUBS condition at some point in their career. A total of 113 cases were described.

Table 4 shows the number of cases seen by the dentists with reference to their number of years of experience. However, it was not possible to demonstrate statistical correlation. This table shows that the number of identified OUBS cases increased with years of practice experience reaching 22% of GDPs after 20-40 years. However, it was not possible to demonstrate a statistical correlation.

Table 4: Clinical experience of GDPs vs No: of cases seen.

| Experience | Number of dentists | Number of OUBS cases | OUBS cases per dentist | Total number of patients in the practice |
|---|---|---|---|---|
| 0-5 years | 17 | 2 | 0.12 | 15810 |
| 6-10 years | 67 | 4 | 0.06 | 123,650 |
| 11-15 years | 113 | 9 | 0.06 | 187,568 |
| 16-20 years | 71 | 4 | 0.06 | 154,800 |
| 21-25years | 53 | 10 | 0.19 | 98,000 |
| 26-30years | 25 | 35 | 1.4 | 40,980 |
| 31-35 years | 20 | 30 | 1.5 | 32,250 |
| 36-40 years | 22 | 14 | 0.64 | 32, 250 |
| 41-45years | 2 | 5 | 2.5 | 8000 |

20 cases (18% of all cases) had been seen by GDPs in the last 2 years, which represented a yearly incidence of 0.0015% or approximately 1 new OUBS case per year per 68 thousand patients not receiving anti-resorptive medications. This, in turn, corresponded to a 2.5% chance each year that a GDP serving this provincial population will see the condition.

Among the 113 cases that were seen there was a high predilection for lingual mandible (78% of cases). This included posterior the lingual mandible with or without mandibular torus involvement. The two major sites at risk were the posterior lingual mandible (46%-no tori) and mandibular or palatal tori (54%).

In 37 cases (32% of cases), conservative management was attempted, which included supportive measures (antimicrobial rinses or antibiotics) or superficial conservative surgical intervention to free the sequestrated bone. All cases resolved although 76 cases (68 % of cases) persisted beyond 8 weeks.

In contrast to the OUBS cases, 12 MRONJ cases were reported by 11 GDPs, all within the two years. This corresponds to approximately 1 new MRONJ case per 114,000 patients. An important note is that the MRONJ cases were derived from observations of the general population, not the subset of the population receiving anti-resorptive medications. The majority of the MRONJ cases (10 cases) were identified in the posterior lingual mandible. Once case occurred on a maxillary exostosis and once case occurred on the mandibular buccal bone.

The OUBS and MRONJ incidence in this study cannot be directly compared. This is because, as noted previously, the MRONJ incidence is obtained from the general population and not from the population using anti-resorptive medications. Further, even though MRONJ was described in the pre-survey informational sessions, it is possible that there was a bias introduced by the educational presentation, which emphasized the research interest in the OUBS presentation. However, these incidence numbers do suggest that a general dentist is more likely to see an OUBS case compared to a MRONJ case.

## 5. Discussion

Since the initial description of OUBS in 1993, there have been several case reports and small case series, which have documented this condition (11). To date, a total of 44 cases (Table 3) have been described. These reports have described the development of an ulcer with an exposed necrotic bone base, which resolved spontaneously or with conservative management involving antimicrobial rinses and/or minor surgical manipulation of the sequestrated bone. A review of these 44 cases indicated that about 18% persisted past 8 weeks after development. Recognition and characterization of the condition was of obvious diagnostic significance and to provide guidance in management. However, because OUBS was typically a self-limiting easily recognized condition with a good prognosis, there was no impetus for further study.

The potential pathologic significance of OUBS changed with introduction of anti-resorptive medications. The clinical similarity to mild cases of MRONJ was soon recognized (2). The similarities included the development of an ulcer with a necrotic bone base, site predilections to lingual mandible and exostoses and the apparently spontaneous development in up to 25 -27 % of MRONJ cases (2, 11,18). Further many (about 18%) of the OUBS cases from the literature search had persisted past the 8 week qualifying period for a MRONJ diagnosis. Thus, a possible relationship between the 2 conditions seemed self-evident and this was acknowledged in a recent major review by the ITJOF (4). The histopathologic and clinical similarities suggested an obvious hypothesis: that OUBS could represent an initiating event for an unknown fraction of the more significant MRONJ cases.

The literature describing ONJ occurring in long bones indicates that it can be caused by a well-defined local traumatic pathway or by non-traumatic pathways involving a range of systemic factors effecting vascularity (See Literature Review, page 20). ONJ presentation in the jaws is not inconsistent with these concepts. However, in the jaws, there is a unique, inherent, anatomic and functional susceptibility to ONJ formation, which has been termed OUBS. We postulate that OUBS in a patient on anti-resorptive medications would have the potential to develop a more significant pathosis characterized by delayed resolution and increased morbidity. This is because the medications interfere with repair and remodeling by affecting osteoclast function. Of significance, in the OUBS concept, the anti-resorptive medications are not directly causal in the development of the condition.

There was a surprising multi-author critique of this suggestion (21). Their points were that the OUBS condition was rare and poorly understood and thus, it should not be included in the MRONJ discussion. Although the critique was rebutted by the ITJOF (22) with reference to the previously noted considerations and also by noting published comments from other prominent clinicians suggesting this was a common condition, the critique did raise a valid point: even though OUBS has been included in standard reference oral pathology textbooks, our understanding is based entirely on case reports and anecdotal accounts. Although these reports have served a useful educational purpose, they have simply confirmed the previously described clinical and histopathologic phenomenology and have not advanced our knowledge regarding etiopathogenesis. There is a lack of comprehensive data regarding the clinical presentation and there is no data at all with respect to incidence. This survey study provides the first data set on OUBS

incidence. It also provides a more comprehensive data set on the duration and site predilection of the condition.

A preliminary study involving review of ONJ cases in the Oral Pathology archives, acquired before the use of anti-resorptive medications was first undertaken to determine how often cases matching the OUBS profile had been submitted. The objective was to determine whether these cases represented a measurable proportion of overall cases showing necrotic bone. These preliminary results revealed 29% were characterized by prolonged bone exposure in the absence of obvious initiating factor. 50% of the identified cases involved spontaneous exposure in the posterior lingual mandible and match the OUBS profile. These results provided suggestive evidence that a survey study was feasible. Subsequently, lessons learned from feedback of a pilot study involving a focus group were very useful in the survey design and resulted in improvements in the survey approach. It became clear that an important part of the survey methodology would be to ensure that each of the respondents had undergone an educational exercise prior to completion of the survey. It was important that the responses reflected informed reliable opinions of qualified primary dental care clinicians. In this regard, multiple analogous survey studies on MRONJ presentations have not tried to ensure that the respondents actually understood the clinical question. In this study, the respondents were asked to indicate only cases which could be clearly identified based on the educational exercise they had completed. They were specifically requested to report negative results. An inducement was offered to encourage clinicians to participate, even in the absence of positive reporting information. This part of the study design was to minimize notoriety bias: the preference by respondents to complete the questionnaire when the respondent

has a significant observation to report. We also collected information regarding the MRONJ cases for patients who currently or had in the past used anti-resorptive medications. Lastly, from the focus groups, it was clear that the survey needed to be easily completed, within minutes. Thus, the survey was designed to fit on a single page and could be easily visualized at first glance, by the respondent. Information regarding age or gender was not collected to simplify the reporting.

Survey results (95% confidence level; 5% interval) were acquired from 391 GDPs representing approximately 20% of all registered GDPs in the province and by extension the informed clinical observations of about 17% of the total Alberta population. The total number of registered GDPs in Alberta registry included dentists, who might practice out of province, are possibly semi-retired or who might not engage in clinical practice such as public health dentists. Thus, the total number of survey respondents was almost certainly higher than the suggested 20% of Alberta GDPs involved in full time general dental practice.

The estimation of the percentage of the Alberta population was based on the GDP estimation of average number of current patients. It did not reflect the total number of unique patients they have seen in their practice lifetime, or acknowledge variations in practice size that may have occurred over the years. It did, however, offer a good estimate of the current surveyed population and thus, the extrapolated incidence figure (obtained from data in the last 2 years) would be a reasonable estimate for the overall population. In this regard, the surveyed population encompassed all ages, including children. Since from the literature review, it seems clear that OUBS is an adult disease, including children

in the survey population would result in a significant underestimation of the actual adult population at risk for OUBS.

A total of 113 cases were identified by 51 respondents (about 13% of all GDPs). 20 cases (18% of all cases) had been seen by GDPs in the last 2 years, which represented a yearly incidence of 0.0015% or approximately 1 new OUBS case per year per 68,000 patients not receiving anti-resorptive medications. Of interest, the MRONJ incidence in patients using oral bisphosphonates has been estimated between 0.0004% and 0.06% (4) and thus, the incidence level of 0.0015% indicated in this study, is comparable to the MRONJ incidence. If the 0.0015% incidence from this study is extrapolated to the total provincial population, the results suggest that there is a 2.5% chance each year that a GDP serving the Alberta population will see the OUBS condition.

In our study, respondents were also asked to indicate MRONJ cases. Our results showed significantly more cases of OUBS (1 OUBS case in 68000) than MRONJ cases (1 in 114,000 cases). It is not reasonable to compare these results because the MRONJ results came from the general population and not from the subset of the population using anti-resorptive medications. Additionally, the study design utilized a pre-survey educational presentation which might have biased the reporting. The pre-survey educational session did describe the MRONJ criteria but emphasized the OUBS criteria; this could have biased respondents to focus on those cases of special interest to the researchers. However, these results, while not offering any insight into MRONJ incidence,

do suggest that an Alberta general dentist is more likely to see a OUBS case compared to a MRONJ case.

The major emphasis of this study was to determine OUBS incidence since this has been the source of repeated speculation and controversy (4,6,18,19). Care was taken to avoid creating a data set which might overstate the incidence. The study was designed to ensure that only those cases which could be reliably assigned to the OUBS category were reported. It was important to accumulate data only from primary care providers with general practices, which accessed the general non-hospitalized population. For this reason, specialists were excluded from the survey although it is quite possible that some affected patients might have directly accessed specialist care and these patients would be lost to the survey. Additionally, some patients might have presented to their physicians, rather than dental care providers. These patients also would be lost to this study. Lastly, it is important to recognize that the patients identified by GDPs, were the ones who presented for diagnosis and management. The study did not identify those patients who developed mild OUBS presentations with a vague unspecified oral pain which spontaneously resolved after a short period. Possibly, these non-presenting patients could even represent a majority of cases. An emphasis was placed on reporting only unequivocal cases, which could have resulted in the loss of further OUBS cases from patients with poorly defined ulcers, not sufficiently distinctive to be retrospectively identified and recalled in this survey study. Further, there was a limitation related to the requirement that the GDPs needed to answer the questionnaire based on their memory of relevant cases. They did not comprehensively review their patient records while completing the questionnaire. All of these considerations strongly suggest that the OUBS

incidence identified in this study most likely understates the real incidence. And lastly, the incidence is derived from the total population, including children. From previous reports, it is clear that the population at risk for OUBS is the adult population. Thus, the OUBS incidence in the “at risk” adult population, again, would be higher than the incidence figure indicated by this study, which included children.

The results confirmed the site predilections suggested by the cumulative data from the 44 cases documented in the OUBS literature review. Our data involving 113 cases confirmed a strong predilection for mandible and exostosis (78% of cases). However, OUBS cases in the literature review were documented in only 16% of cases whereas our data reported in 56% of cases.

Previous case reports provided detailed clinical OUBS descriptions, which were not captured in this global survey study. The case reporting has indicated consistently that the ulcers occurred at the level of the mylohyoid ridge or over exostoses (11-18). This predilection is comparable with MRONJ cases which also show a strong predilection for mandible (73% of cases) as compared to the maxilla of 22.5% and both maxilla and mandible were 4.5% (159). Taken together, the case reporting summarized in the literature review and the survey results of this study show the same anatomic site predilections for OUBS and MRONJ.

The reason for the anatomic predilection is speculative. Since the sites at greatest risk are anatomically exposed with respect to the contiguous oral surfaces, there are suggestions that these sites are at disproportionately greater risk to trauma. Of further relevance, the lamina propria of the mucosa over the exostosis extends directly into the

periosteum, a microanatomic arrangement called a mucoperiosteum. Injury to the mucosa over an exostosis directly impacts the periosteum. In contrast, the mucosa over the mylohyoid ridge represents a transition zone from mucoperiosteum to alveolar mucosa, which is thin and non-keratinized and thus a relatively fragile lining. Again, mucosal ulceration occurring in this site will directly impact vascularization of the dense peripheral cortical bone, resulting in bone necrosis. This form of osteonecrosis (traumatic pathway) was previously discussed in the Literature Review (pg: 20 ) with respect to the long bones. OUBS is a distinctive oral example of ONJ occurring in the traumatic pathway. However, there are further unique local predisposing factors. Since this ONJ event is occurring in the complex, microbial-rich oral environment, there is a constitutive niche for secondary infection of the necrotic bone, which can be efficiently exploited. Any further systemic predilection, which can include a range of debilitative systemic conditions, use of medications impacting the immune response or use of anti-resorptive medications that compromise the host bone reparative response, would further predispose and exacerbate the ONJ condition. However, it is important to note that in this concept, the systemic predilections are not a necessary condition for the ONJ event to occur.

Data on OUBS management confirmed the optimistic prognosis suggested by the published case reporting information. In 26 cases (23%), there was conservative management which included supportive measures such as use of antimicrobial rinses or superficial conservative surgical intervention to free the sequestrated bone. The remaining 87 cases healed spontaneously. Of particular interest, 68% of cases persisted beyond 8 weeks. This was an unexpected high number compared to the OUBS literature

and is significant because this is the widely accepted qualifying time period used to define a MRONJ case. It is unlikely that this represents an accurate estimate of the propensity for OUBS cases to persist. It is considered more likely that this high percentage of cases was documented in the survey because these cases became more memorable. Also, the duration would make it more likely that this subset of patients would be disproportionately more likely to present to their dentist for diagnosis and management. Nevertheless, these survey results and those cases documented in the case report literature clearly indicate that anti-resorptive medication is not necessary for the exposed ulcerated bone to persist past this 8-week qualifying period. Thus, this time sensitive MRONJ diagnostic criteria should not be accorded undue significance.

The implications of the OUBS clinical mimicry with MRONJ, which are documented in this study and the literature review are self-evident. The data from this study provides the first indication of the extent of the “background noise” that the OUBS cases represent and indicate a need to identify and account for obfuscating factors in MRONJ studies. The significance of OUBS as a MRONJ initiating event should be considered. Of possible significance, our study showed a higher number of OUBS cases than MRONJ cases. Although as previously noted, this is not a reflection of differing incidence, it does suggest that a GDP is more likely to see OUBS case than a MRONJ case.

## 6. Conclusions and summary:

This data set represents the first systematic attempt to characterize OUBS presentation and assess incidence. OUBS is an unusual condition, minimally estimated to occur at a 0.0015% yearly incidence in the provincial population. This corresponds to about a 2.5% chance each year that a GDP will encounter the condition. The study confirms the excellent prognosis for OUBS. The study data and the review of the OUBS literature indicates overlap with all of the diagnostic features of MRONJ, including clinical appearance, site predilection and duration. The literature review indicates histopathologic similarities to the sequestrated bone occurring in MRONJ and OUBS. Thus, the possibility that OUBS represent an initiating event for MRONJ needs to be further considered.

**References:**

1. Ruggiero, S.L., Dodson, T.B., & Assael, L.A. et al (2009). American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 Update. *Journal Of Oral And Maxillofacial Surgery 67*(2).
2. Woo, S.B., Hellstein, J.W., & Kalmar J.R. (2006) Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med. 144*, 753–761.
3. Ruggiero, S., Dodson, T., Fantasia, J., Goodday, R., Aghaloo, T., Mehrotra, B., & O'Ryan, F. (2014). American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw—2014 Update. *Journal Of Oral And Maxillofacial Surgery*, 72 (10), 1938-1956. Doi: 10.1016/j.joms.2014.04.03.
4. Khan, A., Morrison , A., Hanley, D., Felsenberg, D., McCauley, L., O'Ryan, F., Reid, I., Ruggiero, S., Taguchi, A ., Tetradis, S., Watts, N., Bradi, M., Peters, E., Guise, T., Eastell, R., Cheung, A., Morin, S., Masri,B.,Cooper, C., Morgan, S., Obermayer-Pietsch, B., Langdahl, B., Al Dabagh, R., Davison, K., Kendler, D., Sandor, G., Josse, R., Bhandari, M., El Rabbany, M., Pierroz, D., Sulimani, R., Saunders, D., Brown, J. and Compston, J.(2015). Diagnosis and Management of Osteonecrosis of the Jaw: A systematic Review and International Consensus. *Journal of Bone and Mineral Research, 30(1),* pp.3-23.

5. Sedghizadeh, P., Stanley, K., Caligiuri, M., Hofkes, S., Lowry, B., & Shuler, C (2009). Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: an institutional inquiry. *Journal Of The American Dental Association,* 140 (1), 61-66 doi: 10.14219/jada.archive.2009.0019.

6. Otto, S. et al. (2011). Osteoporosis and bisphosphonate-related osteonecrosis of the jaw: Not just a sporadic coincidence – a multi-centre study. *J Craniofac Surg 39*, 272-277.

7. Reid I. (2009). Review. Osteonecrosis of the jaw — Who gets it, and why? *Bone 44*, 4-10.

8. Reid, I.R., Cornish, J. (2012). Epidemiology and pathogenesis of osteonecrosis of the jaw. (Review) *Nature Reviews Rheumatology. 8*, 90-96.

9. Kim, H., Kim, J., Kim, S., Lee, S., & Lee, H. (2017). Uncertainty of current algorithm for bisphosphonate-related osteonecrosis of the jaw in population-based studies: a systematic review. *Journal Of Bone And Mineral Research*, 32(3), 584-591. doi: 10.1002/jbmr.3017.

10. Saad, F., Brown, J., Van Poznak, C., Ibrahim, T., Stemmer, S., & Stopeck, A. et al. (2012). Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Annals Of Oncology, 23(*5), 1341-1347. doi: 10.1093/annonc/mdr435.

11. Peters, E., Lovas, G., & Wysocki, G. (1993). Lingual mandibular sequestration and ulceration. *Oral Surgery Oral Medicine¨ Oral Pathology* 75 (6), 739-743. doi:10.1016/0030-4220(93)90433-5.

12. Sonnier, K., & Horning, G. (1997). Spontaneous Bony Exposure: A Report of 4 Cases of Idiopathic Exposure and Sequestration of Alveolar Bone. *Journal of Periodontology, 68(8),* 758-762. doi: 10.1902/jop.1997.68.8.758.

13. Flaitz, C.M. (2000). Oral and maxillofacial pathology case of the month. Lingual mandibular sequestration and ulceration. *Tex Den J 117*(12), 34, 40-41.

14. Kessler, H.P. (2005). Oral and maxillofacial pathology case of the month. Lingual mandibular sequestration with ulceration. *Tex Dent J 122*(2), 198-199, 206-207.

15. Carrard, V.C., Sieck, G.G., Chaves, A.M., Filho, M.S., & Rados, P.V. (2009). Oral ulceration with bone sequestration e case report. *RFO 14*(2), 149-152.

16. Jackson, I., & Maiden, N. (2007). Lingual Mucosal Ulceration with Mandibular Sequestration. *Dental Update*, *34*(9), 573-577. doi: 10.12968/denu.2007.34.9.573

17. Koshal, S., Chaudhry, S., Johnson, A., & Porter, S. (2010). Idiopathic loss of deciduous teeth and associated alveolus. *British Journal Of Oral And Maxillofacial Surgery*, *16*(6), 570. doi: 10.1016/j.bjoms.2011.09.023

18. Scully, C. (2002). Oral ulceration: a new and unusual complication. *British Dental Journal*, *192*(3), 139-140. doi: 10.1038/sj.bdj.4801315a

19. Scully, C.A. (2016). Oral ulceration. *Br Dent J 192*(11), 607.

20. Neville, B. (2016). *Oral and maxillofacial pathology*. St. Louis: Elsevier.

21. Otto,Sven et al. “Comments On Diagnosis And Management of Osteonecrosis Of the Jaw: A Systematic Review And International Consensus”. *Journal Of Bone And Mineral Research*, Vol 30, no.6,2015, pp.1113-1115. Wiley, doi:10.1002/jbmr.2525.

22. Khan, A., Morrison, A., Ruggiero, S., Tetradis, S., Davison, K., Peters, E. and Compston, J. (2015). Response to Comments on “Diagnosis and Management of Osteoporosis of the Jaw: A Systematic Review and International Consensus.” *Journal of Bone and Mineral research, 30(6),*pp. 1116-1117.)

23. Friel, P., & Macintyre, D. (2002). Bone sequestration from lower 3rd molar region. *British Dental Journal 193*(7), 363-366.

24. Taichman, R. (2005). Blood and bone: two tissues whose fates are intertwined to create the hematopoietic stem-cell niche. *Blood, 105(7),* 2631-2639 doi:10.1182/blood-2004-06-2480.

25. Clarke, B. (2008). Normal Bone Anatomy and Physiology. *Clinical Journal Of The American Society Of Nephrology*, 3(Supplement 3), S131-S139. doi: 10.2215/cjn.04151206.

26. Eriksen, E., Axelrod, D., & Melsen, F. (1994). *Bone histomorphometry (pp. 1-12).* New York: Raven Press.

27. Karsenty, G., Kronenberg, H., & Settembre, C. (2009). Genetic Control of Bone Formation. *Annual Review Of Cell And Developmental Biology, 25(1),* 629-648. doi:10.1146/annurev.cellbio.042308.113308.

28. Ottewell, P. (2016). The role of osteoblasts in bone metastasis. *Journal Of Bone Oncology, 5(3),* 124-127. doi: 10.1016/j.jbo.2016.03.007.

29. Xing, L., & Boyce, B. (2005). Regulation of apoptosis in osteoclasts and osteoblastic cells. *Biochemical and Biophysical Research Communications, 328(3),* 709-720. doi:10.1016 / j.bbrc.2004.11.072.

30. Plotkin, L., Aguirre,J., Kousteni, S., Manolagas, S., & Bellido, T. (2005). Bisphosphonates and Estrogens Inhibit Osteocyte Apoptosis via Distinct Molecular Mechanisms Downstream of Extracellular Signal-regulated Kinase Activation. *Journal of Biological Chemistry, 280*(8), 7317-7325. doi: 10.1074/jbc.m412817200.

31. Boyle, W., Simonet, W., & Lacey, D. (2003). Osteoclast differentiation and activation. *Nature, 423*(6937), 337-342. doi:10.1038/nature01658

32. Kobayashi, S., Takahashi, H., Ito, A., Saito, N., Nawata, M., & Horiuchi, H. et al. (2003). Trabecular mini modeling in human iliac bone. *Bone, 32*(2), 163-169.

33. Drake, M., Clarke, B., & Khosla, S. (2008). Bisphosphonates: Mechanism of Action and Role in Clinical Practice. *Mayo Clinic Proceedings, 83*(9), 1032-1045. doi:10.4065/83.9.1032.

34. Russell, R. (2006). Bisphosphonates: From Bench to Bedside. *Annals Of The New York Academy Of Sciences, 1068(1),* 367-401. doi: 10.1196/annals.1346.041.

35. Khan, A. (2008). Bisphosphonate associated osteonecrosis of the jaw. Cam Fam physician. *Canadian Family Physician, 54*(7), 1019-1021.

36. Cremers, S., Pillai, G., & Papapoulos, S. (2005). Pharmacokinetics/ Pharmacodynamics of Bisphosphonates. *Clinical Pharmacokinetics, 44(6)*, 551-570. doi:10.2165/00003088-200544060-00001.

37. Rossini, M., Bianchi, G., Di Munno, O., Giannini, S., Minisola, S., Sinigaglia, L., & Adami, S. (2006). Determinants of adherence to osteoporosis treatment in clinical practice. *Osteoporosis International, 17(6)*, 914-921. doi: 10.1007/s00198-006-0073-6

38. Khosla, S., Burr, D., Cauley, J., Dempster, D., Ebeling, P., & Felsenberg, D. et al. (2007). Bisphosphonate-Associated Osteonecrosis of the Jaw: Report of a Task Force of the American Society for Bone and Mineral Research. *Journal Of Bone And Mineral Research, 22(10),* 1479-1491. doi: 10.1359/jbmr.0707onj

39. Hanley, D., Adachi, J., Bell, A., & Brown, V. (2012). Denosumab: mechanism of action and clinical outcomes. *International Journal Of Clinical Practice, 66*(12), 1139-1146. doi: 10.1111/ijcp.12022.

40. Lippuner, K. (2012). The future of osteoporosis treatment - a research update. *Swiss Medical Weekly*. doi: 10.4414/smw.2012.13624.

41. Rachner, T., Khosla, S., & Hofbauer, L. (2011). New horizons in osteoporosis. *Lancet, 377*(9773), 1276-1287. doi: 10.1016/S0140-6736(10)62349-5.

42. Neville, B. (2016). *Oral and maxillofacial pathology*. St. Louis: Elsevier.

43. Hatzenbuehler, J., & Pulling, T. (2011). Diagnosis and Management of Osteomyelitis. *American Family Physician, 84*(9), 1027-1033.

44. Barrett, A., Lucero, M., Le, T., Robinson, R., Dworkin, R., & Chappell, A. (2007). Epidemiology, Public Health Burden, and Treatment of Diabetic Peripheral Neuropathic Pain: A Review. *Pain Medicine, 8* (suppl 2), S50-S62. doi:10.1111/j.1526-4637.2006.00179.x

45. Tice, A., Hoaglund, P., & Shoultz, D. (2003). Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. *The American Journal Of Medicine, 114(9),* 723-728. doi: 10.1016/s0002-9343(03)00231-6

46. Kushner, G.M., & Alpert, B. (2003). Osteomyelitis and osteoradionecrosis. In: Miloro M, Ghali GE, Larsen PE, Waite PD, eds. Peterson's Principles of Oral and Maxillofacial Surgery. 2nd ed. London: BC Decker. 313-21.

47. Pincus, D., Armstrong, M., & Thaller, S. (2009). Osteomyelitis of the Craniofacial Skeleton. *Seminars In Plastic Surgery, 23*(02), 073-079. doi: 10.1055/s-0029-1214159.

48. Pineda, C., Espinosa, R., & Pena, A. (2009). Radiographic Imaging in Osteomyelitis: The Role of Plain Radiography, Computed Tomography, Ultrasonography, Magnetic Resonance Imaging, and Scintigraphy. *Seminars In Plastic Surgery, 23*(02), 80-89. doi: 10.1055/s-0029-1214160.

49. Pineda, C., Vargas, A., & Rodríguez, A. (2006). Imaging of Osteomyelitis: Current Concepts. *Infectious Disease Clinics Of North America, 20*(4), 789-825. doi:10.1016/j.idc.2006.09.009.

50. Kapoor, A., Page, S., Lavalley, M., Gale, D., & Felson, D. (2007). Magnetic Resonance Imaging for Diagnosing Foot Osteomyelitis. *Archives Of Internal Medicine, 167*(2),125-132. doi: 10.1001/archinte.167.2.125.

51. Termaat, M., Raijmakers, P., Scholten, H., Bakker, F., Patka, P., & Haarman, H. (2005). The Accuracy of Diagnostic Imaging for the Assessment of Chronic Osteomyelitis: A Systematic Review and Meta-Analysis. *The Journal Of Bone And Joint Surgery (American), 87(11),* 2464-2471. doi: 10.2106/jbjs.d.02691

52. Roblot, F., Besnier, J., Juhel, L., Vidal, C., Ragot, S., & Bastides, F. et al. (2007). Optimal Duration of Antibiotic Therapy in Vertebral Osteomyelitis. *Seminars In Arthritis And Rheumatism, 36*(5), 269-277. doi: 10.1016/j.semarthrit.2006.09.004

53. Karamanis, E., Matthaiou, D., Moraitis, L., & Falagas, M. (2008). Fluoroquinolones Versus β-Lactam Based Regimens for the Treatment of Osteomyelitis. *Spine, 33*(10), E297-E304. doi: 10.1097/brs.0b013e31816f6c22

54. Davis, J. (2005). Management of bone and joint infections due to Staphylococcus aureus. *Internal Medicine Journal, 35(*s2), S79-S96. doi: 10.1111/j.1444-0903.2005.00982.x

55. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Retrieved from https://www.niams.nih.gov/

56. Osmani, F., Thakkar, S., & Vigdorchik, J. (2017). The utility of conservative treatment modalities in the management of osteonecrosis: a systematic review. *Bulletin Of The Hospital For Joint Diseases, 75(*3), 186-192.

57. Moya-Angeler, J. (2015). Current concepts on osteonecrosis of the femoral head. *World Journal Of Orthopedics, 6(*8), 590-601. doi: 10.5312/wjo.v6.i8.590

58. Aaron, R.K., & Gray, R. (2007). Osteonecrosis: etiology, natural history, pathophysiology, and diagnosis. In: Callaghan JJ, Rosenberg AG, Rubash HE, editors. The adult hip. Philadelphia: Lippincott Williams & Wilkins. 465–76.

59. Shah, K., Racine, J., Jones, L., & Aaron, R. (2015). Pathophysiology and risk factors for osteonecrosis. *Current Reviews In Musculoskeletal Medicine, 8*(3), 201-209. doi: 10.1007/s12178-015-9277-8

60. Kiaer, T., Pedersen, N., Kristensen, K., & Starklint, H. (1990). Intra-osseous pressure and oxygen tension in avascular necrosis and osteoarthritis of the hip. The Journal Of Bone And Joint Surgery. British Volume, 72-B(6), 1023-1030. doi:10.1302/0301-620x.72b6.2246284

61. Fondi, C., & Franchi, A. (2007). Definition of bone necrosis by the pathologist. *Clinical Cases In Mineral And Bone Metabolism, 4(*1), 21-26.

62. Lai, K., Shen, W., Yang, C., Shao, C., Hsu, J., & Lin, R. (2005). The use of Alendronate to Prevent Early Collapse of the Femoral Head in Patients with Nontraumatic Osteonecrosis. *The Journal Of Bone And Joint Surgery-American Volume,87*(10), 2155-2159. doi: 10.2106/00004623-200510000-00001

63. Nishii, T., Sugano, N., Miki, H., Hashimoto, J., & Yoshikawa, H. (2006). Does Alendronate Prevent Collapse in Osteonecrosis of the Femoral Head?. *Clinical Orthopaedics And Related Research, 443*(:), 273-279. doi: 10.1097/01.blo.0000194078.32776.31

64. Meier, C., Kraenzlin, C., Friederich, N., Wischer, T., Grize, L., Meier, C., & Kraenzlin, M. (2014). Effect of ibandronate on spontaneous osteonecrosis of the knee: a randomized, double-blind, placebo-controlled trial. *Osteoporosis International, 25(*1), 359-366. doi: 10.1007/s00198-013-2581-5

65. Disch, A., Matziolis, G., & Perka, C. (2005). The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost. *The Journal Of Bone And Joint Surgery. British Volume, 87-B(*4), 560-564. doi:10.1302/0301-620x.87b4.15658

66. Pritchett, J. (2001). Statin Therapy Decreases the Risk of Osteonecrosis in Patients Receiving Steroids. *Clinical Orthopaedics And Related Research, 386*, 173-178. doi:10.1097/00003086-200105000-00022

67. Ajmal, M., Matas, A., Kuskowski, M., & Cheng, E. (2009). Does Statin Usage Reduce the Risk of Corticosteroid-Related Osteonecrosis in Renal Transplant Population?. *Orthopedic Clinics Of North America, 40*(2), 235-239. doi: 10.1016/j.ocl.2009.01.004

68. Cartsos, V., Zhu, S., & Zavras, A. (2008). Bisphosphonate Use and the Risk of Adverse Jaw Outcomes. *The Journal Of The American Dental Association, 139*(1), 23-30. doi:10.14219/jada.archive.2008.0016

69. Fellows, J., Rindal, D., Barasch, A., Gullion, C., Rush, W., & Pihlstrom, D. et al. (2011). ONJ in Two Dental Practice-Based Research Network Regions. *Journal Of Dental Research, 90(4),* 433-438. doi: 10.1177/0022034510387795.

70. Grant, B., Amenedo, C., Freeman, K., & Kraut, R. (2008). Outcomes of Placing Dental Implants in Patients Taking Oral Bisphosphonates: A Review of 115 Cases. *Journal Of Oral And Maxillofacial Surgery, 66 (2)*, 223-230. doi: 10.1016/j.joms.2007.09.019.

71. Hong, J., Nam, W., Cha, I., Chung, S., Choi, H., & Kim, K. et al. (2009). Oral bisphosphonate-related osteonecrosis of the jaw: the first report in Asia. *Osteoporosis International, 21*, 847-853. doi: 10.1007/s00198-009-1024-9.

72. Iwamoto, J., Sato, Y., Uzawa, M., Takeda, T., & Matsumoto, H. (2011). Three-year experience with alendronate treatment in postmenopausal osteoporotic Japanese women with or without type 2 diabetes. *Diabetes Research And Clinical Practice, 93(2),*166-173. doi: 10.1016/j.diabres.2011.03.033

73. Lo, J., O'Ryan, F., Gordon, N., Yang, J., Hui, R., & Martin, D. et al. (2010). Prevalence of Osteonecrosis of the Jaw in Patients With Oral Bisphosphonate Exposure. *Journal Of Oral And Maxillofacial Surgery, 68(2)*, 243-253. doi:10.1016/j.joms.2009.03.050.

74. Malden, N., & Lopes, V. (2012). An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence. *Journal Of Bone And Mineral Metabolism, 30(2),* 171-182. doi: 10.1007/s00774-011-0299-z.

75. Mavrokokki, T., Cheng, A., Stein, B., & Goss, A. (2007). Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaws in Australia. *Journal Of Oral And Maxillofacial Surgery, 65*(3), 415-423. doi: 10.1016/j.joms.2006.10.061

76. Taylor, T., Bryant, C., & Popat, S. (2013). A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King's College Hospital. *British Dental Journal, 214*(7), E18. doi:10.1038/sj.bdj.2013.327.

77. Yamazaki, T., Yamori, M., Ishizaki, T., Asai, K., Goto, K., & Takahashi, K. et al. (2012). Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. *International Journal Of Oral And Maxillofacial Surgery, 41*(11), 1397-1403. doi: 10.1016/j.ijom.2012.06.020179.

78. Lyles, K., Colón-Emeric, C., Magaziner, J., Adachi, J., Pieper, C., & Mautalen, C. et al. (2007). Zoledronic acid and clinical fractures and mortality after hip fracture. *The New England Journal Of Medicine, 357(*18), 1799-1809.

79. Powell, D., Bowler, C., Roberts, T., Garton, M., Matthews, C., Mccall, I., & Davie, M. (2012). Incidence of serious side effects with intravenous bisphosphonate: a clinical audit. *QJM, 105(*10), 965-971. doi: 10.1093/qjmed/hcs112.

80. Sieber, P., Lardelli, P., Kraenzlin, C., Kraenzlin, M., & Meier, C. (2013). Intravenous Bisphosphonates for Postmenopausal Osteoporosis: Safety Profiles of Zoledronic Acid and Ibandronate in Clinical Practice. *Clinical Drug Investigation, 33(2),* 117-122. doi:10.1007/s40261-012-0041-1.

81. Felsenberg, D. (2006). Osteonecrosis of the jaw—a potential adverse effect of bisphosphonate treatment. *Nature Clinical Practice Endocrinology & Metabolism, 2(*12), 662-663. doi:10.1038/ncpendmet0348.

82. Khan, A., Rios, L., Sandor, G., Khan, N., Peters, E., & Rahman, M. et al. (2011). Bisphosphonate-associated Osteonecrosis of the Jaw in Ontario: A Survey of Oral and Maxillofacial Surgeons. *The Journal Of Rheumatology, 38(*7), 1396-1402. doi:10.3899/jrheum.100221.

83. Papapoulos, S., Chapurlat, R., Libanati, C., Brandi, M., Brown, J., & Czerwiński, E. et al. (2012). Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension. *Journal Of Bone And Mineral Research, 27*(3), 694-701. doi: 10.1002/jbmr.1479

84. Etminan, M., Aminzadeh, K., Matthew, I., & Brophy, J. (2008). Use of oral bisphosphonates and the risk of aseptic osteonecrosis: a nested case-control study. *The Journal Of Rheumatology, 35(*4), 691-695.

85. Tennis, P., Rothman, K., Bohn, R., Tan, H., Zavras, A., & Laskarides, C. et al. (2012). Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. *Pharmacoepidemiology And Drug Safety, 21*(8), 810-817. doi: 10.1002/pds.3292

86. Grbic, J., Landesberg, R., Lin, S., Mesenbrink, P., Reid, I., & Leung, P. et al. (2008). Incidence of Osteonecrosis of the Jaw in Women With Postmenopausal Osteoporosis in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial. *The Journal Of The American Dental Association, 139(*1), 32-40. doi:10.14219/jada.archive.2008.0017.

87. Orwoll, E., Teglbjærg, C., Langdahl, B., Chapurlat, R., Czerwinski, E., & Kendler, D. et al. (2012). A Randomized, Placebo-Controlled Study of the Effects of Denosumab for the Treatment of Men with Low Bone Mineral Density. *The Journal Of Clinical Endocrinology & Metabolism, 97(*9), 3161-3169. doi: 10.1210/jc.2012-1569.

88. Cummings, S., Martin, J., McClung, M., Siris, E., Eastell, R., & Reid, I. et al. (2009). Denosumab for Prevention of Fractures in Postmenopausal Women With Osteoporosis. *The New England Journal Of Medicine, 361(*8), 756-765. doi:10.1097/01.ogx.0000363236.41902.96.

89. Ulmner, M., Jarnbring, F., & Törring, O. (2014). Osteonecrosis of the Jaw in Sweden Associated With the Oral Use of Bisphosphonate. *Journal Of Oral And Maxillofacial Surgery, 72*(1), 76-82. doi: 10.1016/j.joms.2013.06.221.

90. Grbic, J., Black, D., Lyles, K., Reid, D., Orwoll, E., & McClung, M. et al. (2010). The Incidence of Osteonecrosis of the Jaw in Patients Receiving 5 Milligrams of Zoledronic Acid. *The Journal Of The American Dental Association, 141(*11), 1365-1370. doi:10.14219/jada.archive.2010.0082

91. Zervas, K., Verrou, E., Teleioudis, Z., Vahtsevanos, K., Banti, A., & Mihou, D. et al. (2006). Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. *British Journal Of Haematology, 134(*6), 620-623. doi: 10.1111/j.1365-2141.2006.06230.x

92. Aguiar Bujanda, D., Bohn Sarmiento, U., Cabrera Suarez, M., & Aguiar Morales, J. (2007). Assessment of renal toxicity and osteonecrosis of the jaws in patients receiving zoledronic acid for bone metastasis. *Annals Of Oncology, 18(*3), 556-560. doi:10.1093/annonc/mdl408

93. Aragon-Ching, J., Ning, Y., Chen, C., Latham, L., Guadagnini, J., & Gulley, J. et al. (2009). Higher Incidence of Osteonecrosis of the Jaw (ONJ) in Patients with Metastatic Castration Resistant Prostate Cancer Treated with Anti-Angiogenic Agents. *Cancer Investigation, 27*(2), 221-226. doi: 10.1080/07357900802208608.

94. Assaf, A., Smeets, R., Riecke, B., Weise, E., Gröbe, A., & Blessmann, M. et al. (2013). Incidence of bisphosphonate- related osteonecrosis of the jaw in consideration of primary diseases and concomitant therapies. *Anticancer Research, 33*(9), 3917-3924.

95. Baqain, Z., Sawair, F., Tamimi, Z., Bsoul, N., Al Edwan, G., Almasad, J., & Abbadi, A.(2010). Osteonecrosis of jaws related to intravenous bisphosphonates: the experience of a Jordanian teaching hospital. *The Annals of The Royal College Of Surgeons Of England, 92(6),* 489-494. doi: 10.1308/003588410x12699663903395.

96. Berenson, J., Yellin, O., Boccia, R., Flam, M., Wong, S., & Batuman, O. et al. (2008).Marked improvement in bone mineral density (BMD) for patients (pts) with monoclonal gammopathy of undetermined significance (MGUS) using zoledronic acid (ZOL). *Journal Of Clinical Oncology, 26 (15_suppl)*, 8550-8550. doi:10.1200/jco.2008.26.15_suppl.8550.

97. Bonomi, M., Nortilli, R., Molino, A., Sava, T., Santo, A., Caldara, A., & Cetto, G. (2010). Renal toxicity and osteonecrosis of the jaw in cancer patients treated with bisphosphonates: a long-term retrospective analysis. *Medical Oncology, 27(2),* 224-229. doi: 10.1007/s12032-009-9195-y.

98. Capalbo, S., Delia, M., Diomede, D., Dargenio, M., Chiefa, A., Favia, G., & Liso, V. (2006). Jaw osteonecrosis associated with use of bisphosphonates and chemotherapy: paradoxical complication of treatment of bone lesions in multiple myeloma patients. *International Journal Of Hematology, 83(5),* 439-442. doi: 10.1007/bf03006939.

99. Chang, S., Tenforde, A., Grimsrud, C., O'Ryan, F., Gonzalez, J., & Baer, D. et al. (2012). Atypical femur fractures among breast cancer and multiple myeloma patients receiving intravenous bisphosphonate therapy. *Bone, 51(3),* 524-527. doi:10.1016/j.bone.2012.05.010.

100. Clarke, B., Boyette, J., Vurai, E., Suen, J., Anaissie, E., & Stack, B. (2007). Bisphosphonates and jaw osteonecrosis: the UAMS experience. *Otolaryngol Head Neck Surgery, 136(3),* 396-400.

101. Dimopoulos, M., Kastritis, E., Anagnostopoulos, A., Melakopoulos, I., Gika, D., & Moulopoulos, L. et al. (2006). Osteonec-rosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica, 91*(7), 968-971. doi: 10.1093/annonc/mdn554.

102. Estilo, C., Van Poznak, C., Wiliams, T., Bohle, G., Lwin, P., & Zhou, Q. et al. (2008). Osteonecrosis of the Maxilla and Mandible in Patients with Advanced Cancer Treated with Bisphosphonate Therapy. *The Oncologist*, *13*(8), 911-920. doi: 10.1634/theoncologist.2008-0091

103. Guarneri, V., Donati, S., Nicolini, M., Giovannelli, S., D'Amico, R., & Conte, P. (2005). Renal Safety and Efficacy of i.v. Bisphosphonates in Patients with Skeletal Metastases Treated for up to 10 Years. *The Oncologist*, *10*(10), 842-848. doi: 10.1634/theoncologist.10-10-842

104. Mauri, D., Valachis, A., Polyzos, I., Polyzos, N., Kamposioras, K., & Pesce, L. (2009). Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a metanalysis. *Breast Cancer Research And Treatment*, *116*(3), 433-439. doi: 10.1007/s10549-009-0432-z

105. Orita, Y., Sugitani, I., Toda, K., Manabe, J., & Fujimoto, Y. (2011). Zoledronic Acid in the Treatment of Bone Metastases from Differentiated Thyroid Carcinoma. *Thyroid*, *21*(1), 31-35. doi: 10.1089/thy.2010.0169

106. Smidt-Hansen, T., Folkmar, T., Fode, K., Agerbaek, M., & Donskov, F. (2013). Combination of Zoledronic Acid and Targeted Therapy Is Active But May Induce Osteonecrosis of the Jaw in Patients With Metastatic Renal Cell Carcinoma. *Journal Of Oral And Maxillofacial Surgery*, *71*(9), 1532-1540. doi: 10.1016/j.joms.2013.03.019

107. Walter, C., Al-Nawas, B., du Bois, A., Buch, L., Harter, P., & Grötz, K. (2009). Incidence of bisphosphonate-associated osteonecrosis of the jaws in breast cancer patients. *Cancer*, *115*(8), 1631-1637. doi: 10.1002/cncr.24119

108. Young, J., Nickman, N., Biskupiak, J., Barney, R., Gaffney, D., Namjoshi, M., & Brandt, P. (2013). Characterization of clinical course and usual care patterns in female metastatic breast cancer patients treated with zoledronic acid. *The Breast*, *22*(4), 495-503. doi: 10.1016/j.breast.2012.09.012

109. Berenson, J., Yellin, O., Crowley, J., Makary, A., Gravenor, D., & Yang, H. et al. (2011). Prognostic factors and jaw and renal complications among multiple myeloma patients treated with zoledronic acid. *American Journal Of Hematology*, *86*(1), 25-30. doi: 10.1002/ajh.21912

110. Beuselinck, B., Wolter, P., Karadimou, A., Elaidi, R., Dumez, H., & Rogiers, A. et al. (2012). Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases. *British Journal Of Cancer*, *107*(10), 1665-1671. doi: 10.1038/bjc.2012.385

111. Francini, F., Pascucci, A., Francini, E., Miano, S., Bargagli, G., Ruggiero, G., & Petrioli, R. (2011). Osteonecrosis of the jaw in patients with cancer who received zoledronic acid and bevacizumab. *The Journal Of The American Dental Association*, *142*(5), 506-513. doi: 10.14219/jada.archive.2011.0220

112. Ganguly, S., Divine, C., Aljitawi, O., Abhyankar, S., McGuirk, J., & Graves, L. (2012). Prophylactic use of zoledronic acid to prevent early bone loss is safe and feasible in patients with acute myeloid leukemia undergoing allogeneic stem cell transplantation. *Clinical Transplantation*, *26*(3), 447-453. doi: 10.1111/j.1399-0012.2011.01527.x

113. Hoff, A., Toth, B., Altundag, K., Johnson, M., Warneke, C., & Hu, M. et al. (2008). Frequency and Risk Factors Associated With Osteonecrosis of the Jaw in Cancer Patients Treated With Intravenous Bisphosphonates. *Journal Of Bone And Mineral Research*, *23*(6), 826-836. doi: 10.1359/jbmr.080205

114. Jadu, F., Lee, L., Pharoah, M., Reece, D., & Wang, L. (2007). A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. *Annals Of Oncology*, *18*(12), 2015-2019. doi: 10.1093/annonc/mdm370

115. Walter, C., Al-Nawas, B., Grötz, K., Thomas, C., Thüroff, J., & Zinser, V. et al. (2008). Prevalence and Risk Factors of Bisphosphonate-Associated Osteonecrosis of the Jaw in Prostate Cancer Patients with Advanced Disease Treated with Zoledronate. *European Urology*, *54*(5), 1066-1072. doi: 10.1016/j.eururo.2008.06.070

116. Scoletta, M., Arduino, P., Pol, R., Arata, V., Silvestri, S., Chiecchio, A., & Mozzati, M. (2011). Initial Experience on the Outcome of Teeth Extractions in Intravenous Bisphosphonate-Treated Patients: A Cautionary Report. *Journal Of Oral And Maxillofacial Surgery*, *69*(2), 456-462. doi: 10.1016/j.joms.2010.07.026

117. Amadori, D., Aglietta, M., Alessi, B., Gianni, L., Ibrahim, T., & Farina, G. et al. (2013). Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. *The Lancet Oncology*, *14*(7), 663-670. doi: 10.1016/s1470-2045(13)70174-8

118. Bamias, A., Kastritis, E., Bamia, C., Moulopoulos, L., Melakopoulos, I., & Bozas, G. et al. (2005). Osteonecrosis of the Jaw in Cancer After Treatment With Bisphosphonates: Incidence and Risk Factors. *Journal Of Clinical Oncology*, *23*(34), 8580-8587. doi: 10.1200/jco.2005.02.8670

119. Barrett-Lee, P., Casbard, A., Abraham, J., Hood, K., Coleman, R., & Simmonds, P. et al. (2014). Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. *The Lancet Oncology*, *15*(1), 114-122. doi: 10.1016/s1470-2045(13)70539-4

120. Boonyapakorn, T., Schirmer, I., Reichart, P., Sturm, I., & Massenkeil, G. (2008). Bisphosphonate-induced osteonecrosis of the jaws: Prospective study of 80 patients with multiple myeloma and other malignancies. *Oral Oncology*, *44*(9), 857-869. doi: 10.1016/j.oraloncology.2007.11.012

121. Cafro, A., Barbarano, L., Nosari, A., D'Avanzo, G., Nichelatti, M., & Bibas, M. et al. (2008). Osteonecrosis of the Jaw in Patients with Multiple Myeloma Treated with Bisphosphonates: Definition and Management of the Risk Related to Zoledronic Acid. *Clinical Lymphoma And Myeloma*, *8*(2), 111-116. doi: 10.3816/clm.2008.n.013

122. Christodoulou, C., Pervena, A., Klouvas, G., Galani, E., Falagas, M., & Tsakalos, G. et al. (2009). Combination of Bisphosphonates and Antiangiogenic Factors Induces Osteonecrosis of the Jaw More Frequently than Bisphosphonates Alone. *Oncology*, *76*(3), 209-211. doi: 10.1159/000201931

123. Coleman, R., Woodward, E., Brown, J., Cameron, D., Bell, R., & Dodwell, D. et al. (2011). Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE–BIG 01–04) for women with stage II/III breast cancer. *Breast Cancer Research Treatment*, *48*(1), 429-438. doi: 10.1016/j.bone.2010.10.079

124. Coleman, R., Marshall, H., Cameron, D., Dodwell, D., Burkinshaw, R., & Keane, M. et al. (2011). Breast-cancer adjuvant therapy with zoledronic acid. *The New England Journal Of Medicine*, *365*(15), 1396-1405. doi: 10.1056/NEJMoa1105195

125. Corso, A., Varettoni, M., Zappasodi, P., Klersy, C., Mangiacavalli, S., Pica, G., & Lazzarino, M. (2007). A different schedule of zoledronic acid can reduce the risk of the osteonecrosis of the jaw in patients with multiple myeloma. *Leukemia*, *21*(7), 1545-1548. doi: 10.1038/sj.leu.2404682

126. Crawford, B., McNulty, R., Kraut, E., & Turowski, R. (2009). Extended Use of Intravenous Bisphosphonate Therapy for the Prevention of Skeletal Complications in Patients with Cancer. *Cancer Investigation*, *27*(10), 984-988. doi: 10.3109/07357900902783203

127. Dimopoulos, M., Kastritis, E., Bamia, C., Melakopoulos, I., Gika, D., & Roussou, M. et al. (2009). Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Annals Of Oncology*, *20*(1), 117-120. doi: 10.1093/annonc/mdn554

128. Ding, X., Fan, Y., Ma, F., Li, Q., Wang, J., & Zhang, P. et al. (2012). Prolonged administration of bisphosphonates is well-tolerated and effective for skeletal-related events in Chinese breast cancer patients with bone metastasis. *The Breast*, *21*(4), 544-549. doi: 10.1016/j.breast.2012.04.008

129. Fizazi, K., Carducci, M., Smith, M., Damião, R., Brown, J., & Karsh, L. et al. (2011). Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *The Lancet*, *377*(9768), 813-822. doi: 10.1016/s0140-6736(10)62344-6

130. Gimsing, P., Carlson, K., Turesson, I., Fayers, P., Waage, A., & Vangsted, A. et al. (2010). Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. *The Lancet Oncology*, *11*(10), 973-982. doi: 10.1016/s1470-2045(10)70198-4

131. Haidar, A., Jønier, M., Folkmar, T., & Lund, L. (2009). Bisphosphonate (zoledronic acid)-induced osteonecrosis of the jaw. *Scandinavian Journal Of Urology And Nephrology*, *43*(6), 442-444. doi: 10.3109/00365590903295193

132. Henry, D., Costa, L., Goldwasser, F., Hirsh, V., Hungria, V., & Prausova, J. et al. (2011). Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. *Journal Of Clinical Oncology*, *29*(9), 1125-1132. doi: 10.1200/jco.2010.31.3304

133. Hines, S., Mincey, B., Dentchev, T., Sloan, J., Perez, E., & Johnson, D. et al. (2009). Immediate versus delayed zoledronic acid for prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen-N03CC. Breast Cancer Research And Treatment, 117(3), 603-609. doi: 10.1007/s10549-009-0332-2

134. Ibrahim, T., Barbanti, F., Giorgio-Marrano, G., Mercatali, L., Ronconi, S., Vicini, C., & Amadori, D. (2008). Osteonecrosis of the Jaw in Patients with Bone Metastases Treated with Bisphosphonates: A Retrospective Study. *The Oncologist*, *13*(3), 330-336. doi: 10.1634/theoncologist.2007-0159

135. Kucukzeybek, Y., Gorumlu, G., Cengiz, E., Erten, C., Karaca, B., & Gul, M. et al. (2010). Bisphosphonate (zoledronic acid) associated adverse events: single center experience. *International Journal Of Hematology And Oncology*, *20*(3), 135-140. Retrieved from http://www.uhod.org/pdf/PDF_414.pdf

136. La Verde, N., Bareggi, C., Garassino, M., Borgonovo, K., Sburlati, P., & Pedretti, D. et al. (2008). Osteonecrosis of the jaw (ONJ) in cancer patients treated with Bisphosphonates: how the knowledge of a phenomenon can change its evolution. *Supportive Care In Cancer*, *16*(11), 1311-1315. doi: 10.1007/s00520-008-0484-3

137. Miyazaki, H., Nishimatsu, H., Kume, H., Suzuki, M., Fujimura, T., & Fukuhara, H. et al. (2012). Leukopenia as a risk factor for osteonecrosis of the jaw in metastatic prostate cancer treated using zoledronic acid and docetaxel. *BJU International*, *110*(11b), E520-E525. doi: 10.1111/j.1464-410x.2012.11205.x

138. Morgan, G., Davies, F., Gregory, W., Cocks, K., Bell, S., & Szubert, A. et al. (2010). First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *The Lancet*, *376*(9757), 1989-1999. doi: 10.1016/s0140-6736(10)62051-x

139. Musto, P., Petrucci, M., Bringhen, S., Guglielmelli, T., Caravita, T., & Bongarzoni, V. et al. (2008). A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. *Cancer*, *113*(7), 1588-1595. doi: 10.1002/cncr.23783

140. Nicolatou-Galitis, O., Papadopoulou, E., Sarri, T., Boziari, P., Karayianni, A., & Kyrtsonis, M. et al. (2011). Osteonecrosis of the jaw in oncology patients treated with bisphosphonates: prospective experience of a dental oncology referral center. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, And Endodontology*, *112*(2), 195-202. doi: 10.1016/j.tripleo.2011.02.037

141. Ortega, C., Montemurro, F., Faggiuolo, R., Vormola, R., Nanni, D., & Goia, F. et al. (2007). Osteonecrosis of the jaw in prostate cancer patients with bone metastases treated with zoledronate: A retrospective analysis. *Acta Oncologica*, *46*(5), 664-668. doi: 10.1080/02841860601185917

142. Rathbone, E., Brown, J., Marshall, H., Collinson, M., Liversedge, V., & Murden, G. et al. (2013). Osteonecrosis of the Jaw and Oral Health–Related Quality of Life After Adjuvant Zoledronic Acid: An Adjuvant Zoledronic Acid to Reduce Recurrence Trial Subprotocol (BIG01/04). *Journal Of Clinical Oncology*, *31*(21), 2685-2691. doi: 10.1200/jco.2012.46.4792

143. Ria, R., Reale, A., Moschetta, M., Mangialardi, G., Dammacco, F., & Vacca, A. (2013). A retrospective study of skeletal and disease-free survival benefits of zoledronic acid therapy in patients with multiple myeloma treated with novel agents. *International Journal of Clinical and Experimental Medicine*, *6*(1), 30–38.

144. Sanna, G., Preda, L., Bruschini, R., Cossu Rocca, M., Ferretti, S., & Adamoli, L. et al. (2006). Bisphosphonates and jaw osteonecrosis in patients with advanced breast cancer. *Annals Of Oncology*, *17*(10), 1512-1516. doi: 10.1093/annonc/mdl163

145. Scagliotti, G., Hirsh, V., Siena, S., Henry, D., Woll, P., & Manegold, C. et al. (2012). Overall Survival Improvement in Patients with Lung Cancer and Bone Metastases Treated with Denosumab Versus Zoledronic Acid: Subgroup Analysis from a Randomized Phase 3 Study. *Journal Of Thoracic Oncology*, *7*(12), 1823-1829. doi: 10.1097/jto.0b013e31826aec2b

146. Scagliotti, G., Kosmidis, P., de Marinis, F., Schreurs, A., Albert, I., & Engel-Riedel, W. et al. (2012). Zoledronic acid in patients with stage IIIA/B NSCLC: results of a randomized, phase III study. *Annals Of Oncology*, *23*(8), 2082-2087. doi: 10.1093/annonc/mds128

147. Tassinari, D., Poggi, B., Nicoletti, S., Fantini, M., Tamburini, E., Possenti, C., & Sartori, S. (2007). Zoledronic Acid Treatment at Home: Safety Data from an Observational Prospective Trial. *Journal Of Palliative Medicine*, *10*(2), 352-358. doi: 10.1089/jpm.2006.0122

148. Wang, E., Kaban, L., Strewler, G., Raje, N., & Troulis, M. (2007). Incidence of Osteonecrosis of the Jaw in Patients With Multiple Myeloma and Breast or Prostate Cancer on Intravenous Bisphosphonate Therapy. *Journal Of Oral And Maxillofacial Surgery*, *65*(7), 1328-1331. doi: 10.1016/j.joms.2007.03.006

149. Fizazi, K., Lipton, A., Mariette, X., Body, J., Rahim, Y., & Gralow, J. et al. (2009). Randomized Phase II Trial of Denosumab in Patients With Bone Metastases From Prostate Cancer, Breast Cancer, or Other Neoplasms After Intravenous Bisphosphonates. *Journal Of Clinical Oncology*, *27*(10), 1564-1571. doi: 10.1200/jco.2008.19.2146

150. Lipton, A., Steger, G., Figueroa, J., Alvarado, C., Solal-Celigny, P., & Body, J. et al. (2008). Extended Efficacy and Safety of Denosumab in Breast Cancer Patients with Bone Metastases Not Receiving Prior Bisphosphonate Therapy. *Clinical Cancer Research*, *14*(20), 6690-6696. doi: 10.1158/1078-0432.ccr-07-5234

151. Smith, M., Egerdie, B., Toriz, N., Feldman, R., Tammela, T., & Saad, F. et al. (2009). Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *The New England Journal Of Medicine*, *361*(8), 745-755. doi: 10.1056/NEJMoa0809003

152. Walter, C., Al-Nawas, B., Frickhofen, N., Gamm, H., Beck, J., & Reinsch, L. et al. (2010). Prevalence of bisphosphonate associated osteonecrosis of the jaws in multiple myeloma patients. *Head & Face Medicine*, *6*(1), 11. doi: 10.1186/1746-160x-6-11

153. Aviles, A., Neri, N., Huerta-Guzman, J., & Nambo, M. (2013). Randomized clinical trial of zoledronic acid in multiple myeloma patients undergoing high-dose chemotherapy and stem-cell transplantation. *Current Oncology*, *20*(1), 13-20. doi: 10.3747/co.20.1055

154. Gnant, M., Mlineritsch, B., Stoeger, H., Luschin-Ebengreuth, G., Heck, D., & Menzel, C. et al. (2011). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *The Lancet Oncology*, *12*(7), 631-641. doi: 10.1016/s1470-2045(11)70122-x

155. Israeli, R., Rosenberg, S., Saltzstein, D., Gottesman, J., Goldstein, H., & Hull, G. et al. (2007). The Effect of Zoledronic Acid on Bone Mineral Density in Patients Undergoing Androgen Deprivation Therapy. *Clinical Genitourinary Cancer*, *5*(4), 271-277. doi: 10.3816/cgc.2007.n.003

156. Safra, T., Bernstein-Molho, R., Greenberg, J., Pelles-Avraham, S., Stephansky, I., & Sarid, D. et al. (2011). The Protective Effect of Zoledronic Acid on Bone Loss in Postmenopausal Women with Early Breast Cancer Treated with Sequential Tamoxifen and Letrozole: A Prospective, Randomized, Phase II Trial. *Oncology*, *81*(5-6), 298-305. doi: 10.1159/000334456

157. Von Minckwitz, G., Zahm, M., Eidtmann, H., Tesch, H., du Bois, A., & Schwedler, K. et al. (2010). 24 Zoledronic acid (ZOL) as add-on therapy in patients with tumour residuals after neoadjuvant chemotherapy for primary breast cancer – first interim safety analysis of the NATAN study (GBG 36). *European Journal Of Cancer Supplements*, *8*(3), 65. doi: 10.1016/s1359-6349(10)70055-0

158. Smith, M., Saad, F., Coleman, R., Shore, N., Fizazi, K., & Tombal, B. et al. (2012). Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *The Lancet*, *379*(9810), 39-46. doi: 10.1016/s0140-6736(11)61226-9

159. Vahtsevanos, K., Kyrgidis, A., Verrou, E., Katodritou, E., Triaridis, S., & Andreadis, C. et al. (2009). Longitudinal Cohort Study of Risk Factors in Cancer Patients of Bisphosphonate-Related Osteonecrosis of the Jaw. *Journal Of Clinical Oncology*, *27*(32), 5356-5362. doi: 10.1200/jco.2009.21.9584

160. Qi, W., Tang, L., He, A., Yao, Y., & Shen, Z. (2014). Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. *International Journal Of Clinical Oncology*, *19*(2), 403-410. doi: 10.1007/s10147-013-0561-6

161. Kunchur, R., Need, A., Hughes, T., & Goss, A. (2009). Clinical Investigation of C-Terminal Cross-Linking Telopeptide Test in Prevention and Management of Bisphosphonate-Associated Osteonecrosis of the Jaws. *Journal Of Oral And Maxillofacial Surgery*, *67*(6), 1167-1173. doi: 10.1016/j.joms.2009.02.004

162. Fehm, T., Beck, V., Banys, M., Lipp, H., Hairass, M., & Reinert, S. et al. (2009). Bisphosphonate-induced osteonecrosis of the jaw (ONJ): Incidence and risk factors in patients with breast cancer and gynecological malignancies. *Gynecologic Oncology*, *112*(3), 605-609. doi: 10.1016/j.ygyno.2008.11.029

163. Kyrgidis, A., Vahtsevanos, K., Koloutsos, G., Andreadis, C., Boukovinas, I., & Teleioudis, Z. et al. (2008). Bisphosphonate-Related Osteonecrosis of the Jaws: A Case-Control Study of Risk Factors in Breast Cancer Patients. *Journal Of Clinical Oncology*, *26*(28), 4634-4638. doi: 10.1200/jco.2008.16.2768

164. Mozzati, M., Arata, V., & Gallesio, G. (2012). Tooth extraction in patients on zoledronic acid therapy. *Oral Oncology*, *48*(9), 817-821. doi: 10.1016/j.oraloncology.2012.03.009

165. Scoletta, M., Arata, V., Arduino, P., Lerda, E., Chiecchio, A., & Gallesio, G. et al. (2013). Tooth Extractions in Intravenous Bisphosphonate-Treated Patients: A Refined Protocol. *Journal Of Oral And Maxillofacial Surgery*, *71*(6), 994-999. doi: 10.1016/j.joms.2013.01.006

166. Tsao, C., Darby, I., Ebeling, P., Walsh, K., O'Brien-Simpson, N., Reynolds, E., & Borromeo, G. (2013). Oral Health Risk Factors for Bisphosphonate-Associated Jaw Osteonecrosis. *Journal Of Oral And Maxillofacial Surgery*, *71*(8), 1360-1366. doi: 10.1016/j.joms.2013.02.016

167. Almazrooa, S., Chen, K., Nascimben, L., Woo, S., & Treister, N. (2010). Osteonecrosis of the Mandible After Laryngoscopy and Endotracheal Tube Placement. *Anesthesia & Analgesia*, *111*(2), 437-441. doi: 10.1213/ane.0b013e3181e0cdcd

168. Farah, C., & Savage, N. (2003). Oral ulceration with bone sequestration. Australian Dental Journal , 48 (1), 61-64. doi: 10.1111/j.1834-7819.2003.tb00011.x

169. Chanavaz, M. (1995). Anatomy and histophysiology of the periosteum: quantification of the periosteal blood supply to the adjacent bone with 85Sr and gamma spectrometry. J Oral Implantol, 21(3), 214-219. doi: 10.1111/j.1834-7819.1988.tb00650.x

170. Gadiwalla, Y., & Patel, V. (2018). Osteonecrosis of the jaw unrelated to medication or radiotherapy. Oral Surgery, Oral Medicine, Oral Pathology And Oral Radiology, 125(5), 446-453. doi: 10.1016/j.oooo.2017.12.016

171. Peters E., Lovas G.L & Wysocki G.P. (1993).Lingual mandibular sequestration and ulceration. *Oral surgery,oral medicine and oral pathology,75,* 739-743.

172. Gunduz K., Ozden B., Kurt M., Bulut E., & Gunhan O. (2010). Lingual mandibular bone sequestration : A case report. *J Dent Fac Ataturk Univ Dis Hek Fak Derg (sup. 3)*, 1-4.

173. Villa A. & Gohel A.(2014). Oral ulceration with mandibular necrosis. *Journal of the American Dental Association*,145,752-756.

174. Kharazzmi M., Nilsson U. & Hallberg P(2017). Case report: Osteonecrosis as a complication of GA. *British dental Journal, 222,645.*

175. Alkabouli J., Kokovic V. &Emad A. (2016). Post extraction lingual mucosal ulceration with bone necrosis. *The Saudi Journal for Dental research,7,*34-37.

176. Kharazmi, M. “Mandibular bone exposure and osteonecrosis as a complication of general anesthesia. *Upsala Journal of medical sciences, 120*, 215-216.

177. Gabric D., Seiwerth S., Baraba A., Vucicevic V. & Boras (2017). Mandibular Osteonecrosis due to the Pulpal-Periodontal Syndrome: A Case Report and Review of the Literature. *Acta stomatologica Croatica*, 51,65-71.

178. Cerruto C., Ugolini a., & Cozzani M. (2018). Lingual mandibular necrosis after dental impressions for orthodontic study models. American journal of orthodontics and dentofacial orthopedics : official publication of the *American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 153*,445-448.

179. Marx, R. (2003). Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *Journal Of Oral And Maxillofacial Surgery, 61(9),* 1115-1117. doi: 10.1016/s0278-2391(03)00720-1.

# Appendix 1

**Methods and Results of the preliminary study:**

**Methods:**

- All cases of jaw sequestration submitted over a 3 year period (1988-90), before use of bisphosphonates, were reviewed. Clinical histories were required for inclusion.

- Age, gender, site, associated anatomic factors, clinical appearance, clinical diagnosis, lesion duration before surgery and histopathologic presentation were assessed.

- A subset of cases presenting with exposed bone were identified and from these, a further group of cases was separated in which the exposed bone had been present for more than 8 weeks. The latter group matched the MRONJ clinical presentation profile but without the further history of bisphosphonate exposure.

- The fraction of BRONJ like cases compared to other sequestrations was determined and the clinical characteristics of these cases were assessed.

**Results**

-48 sequestration cases with clinical histories (mean age = 45.7; SD = 18.2) were identified. There was a 64 % male predilection.

-34 cases (71%) could be attributed to a range of etiologic factors (post- surgical complications, infection, trauma, radiation, eruption sequestrae) and did not match the MRONJ–like profile.

-14 cases (29%) were characterized by prolonged bone exposure in the absence of a clinically obvious initiating factor. (mean age = 54.3.5; SD=17.4; 57% male).

- 7 cases involved spontaneous exposure in the posterior lingual mandible.

  -4 cases occurred in association with developmental exostoses

  -Mandibular torus-2

  - Buccal exostosis -1

  - Palatal exostosis-1

  -3 cases were associated with persistent recessed gingiva.

- In 7 of the idiopathic, prolonged bone exposure cases, there was definitive information regarding duration of the lesion before surgical management.

- 2 cases from lingual mandible and 1 from recessed gingiva (43% of total exposed bone cases) had persisted for over 8 weeks before surgical management. (mean age=49.3; SD= 11.0; 2F,1M). These BRONJ-like cases represented 6% of total sequestration cases.

The other 4 cases were surgically resolved before the 8week limit.

# Appendix 2

UNIVERSITY OF ALBERTA

FACULTY OF MEDICINE & DENTISTRY
SCHOOL OF DENTISTRY

Oral Pathology and Oral Medicine
5-316 Edmonton Clinic Health Academy
Edmonton, Alberta, T6G 1C9

**Title of Study:** **Survey of OSTEONECROSIS OF THE JAWS NOT ASSOCIATED WITH ANTI-RESORPTIVE BONE MEDICATIONS**

**Principal investigator:** Dr. Vandana Singh Phone number: 780---------
**Supervisor:** Dr. Edmund Peters Phone number 780 492 1338

There are five major forms of antiresorptive therapy used to increase bone strength in patients with osteoporosis. The five groups include estrogens, selective estrogen receptor modulators, calcitonin, monoclonal antibodies such as denosumab and bisphosphonates. *Common examples of the bisphosphonate drugs are alendronate (Fosamax ®), etidronate (Didrocal ®), risedronate (Actonel ®) and zoledronic acid (Aclasta®). A rare bone complication that can occur in patient using anti-resorptive medication is called* ***medication related osteonecrosis of the jaws (MRONJ).***

MRONJ cases are defined as follows:

(1) Current or previous treatment with anti-resorptive or angiogenic agents
(2) Exposed bone or bone that can be probed through an intraoral or extra oral fistula in the maxillofacial region, which has persisted for more than 8 weeks
(3) No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

It is possible for jaw osteonecrosis, **having the same clinical appearance as MRONJ**, to occur in patient who **do not use anti-resorptive medications**. These cases appear to occur most commonly in the posterior lingual mandible or in association with exostoses such as mandibular or maxillary tori. Healing of the ulcer occurs after the non-vital bone base sloughs away spontaneously or in some cases, conservative surgical removal might be necessary. If you are interested, a short tutorial with images is available at this website: ----------

**Although well recognized, we have no information on how commonly this condition occurs and our understanding is based on case reports or short case series.**

You are invited to participate in a short one page survey. It asks if you have seen patients with jaw osteonecrosis **not related to anti-resorptive medications.** There is a short series of questions to help us understand how the biologic behavior of the lesion and how common it is.

**The survey is confidential.** *A faxed response is requested.* When the faxed response is received, the submitting office will be checked off a list indicating that the office has answered the survey. When all responses have been received, data from the anonymous surveys will be compiled. The responses will be presented as aggregated findings. There are no known risks or benefits from participating in this study.

Our study has been reviewed for its ethical guidelines, and approved by the **Research Ethics Board** at the University of Alberta. If you have any questions about the rights you have as a participant in this study, you may contact the Health Research Ethics Board at (780) 492-2615. This office has no affiliation with the study investigators. The investigators do not have any conflicts of interest with this study

We hope that you will participate in this study. If you have any questions, either now or later, please contact either of us. Our phone numbers are indicated above. Thank you for your help with this study!

# Appendix 3

UNIVERSITY OF ALBERTA

FACULTY OF MEDICINE & DENTISTRY
SCHOOL OF DENTISTRY

Oral Pathology and Oral Medicine
5-316 Edmonton Clinic Health Academy
Edmonton, Alberta, T6G 1C9

**Title of Study:** **Survey of OSTEONECROSIS OF THE JAWS NOT ASSOCIATED WITH ANTI-RESORPTIVE BONE MEDICATIONS**

**Principal investigator:** Dr. Vandana Singh Phone number: 7804075561
**Supervisor:** Dr. Edmund Peters Phone number 780 492 1338

**Each form should represent the experience of one clinician only. If there is more than one clinician in the practice, please copy the form or fax us a note asking for additional surveys.**
*(Osteonecrosis of jaws not associated with anti-resorptive medication = **OJNAAM)***

1. How many years have you engaged in clinical practice?_____
2. What has been the average number of patients in your care each year?_____
3. Have you **ever** seen osteonecrosis of the jaw in patients who are **not** taking anti-resorptive bone medications (an OJNAAM case)? Yes or No.

**If you answered yes, please answer 4a to 4f. If you answered no, go to on to Question 5.**

4. a) How many OJNAAM cases have you ever seen? _____
   b) How many OJNAAM cases have you seen in the last 2 years? _____
   c) How many of the total cases occurred in association with a bone exostosis? _____
      - What type of exostosis (mandibular or maxillary torus, buccal exostosis) was associated with the OJNAAM? _____
   d) For the cases not associated with the exostosis, where in the jaws did each case occur? Please be specific.
      _____
      _____
   e) For each case, how long after onset of the lesion did it take before the lesion resolved?
      _____
   f) For each case, did the lesion resolve spontaneously or did you medicate or mange the case surgically?
      _____

5. Have you ever seen ONJ cases in patients **using** anti resorptive medication? Yes or no

If yes:
How many cases have you seen? _____
How many cases have you seen in the last 2 years? _____
Were the patients being treated for a cancer?
Where in the jaws did the cases occur? _____
Did the case occur in association with an exostosis? _____-
How long did they last and how were they treated?

Thank you for completing the survey!
Please fax your completed survey to: 780-407-5701

## Appendix 4a

# INCIDENCE OF JAW OSTEONECROSIS NOT ASSOCIATED WITH ANTI-RESORPTIVE MEDICATION

Dr. Vandana Singh
Dr. Edmund Peters

- **Osteonecrosis:** A disease in which a temporary or permanent loss of the blood supply to the jaw bone causes the tissue to die and the bone to collapse.
- **Oral ulceration with bone sequestration:** Identified in 1993. The condition occurs as painful ulceration generally involving the posterior lingual mandible at the level of mylohyoid ridge. The ulcer can persist for weeks to months.

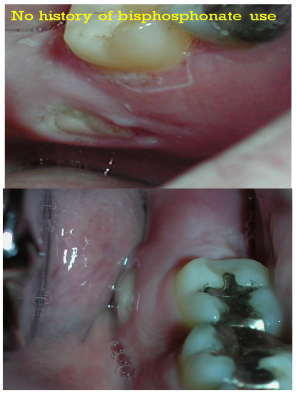
Occurs in absence of systemic disease or anti-resorptive therapy. Pathogenesis is not well understood.

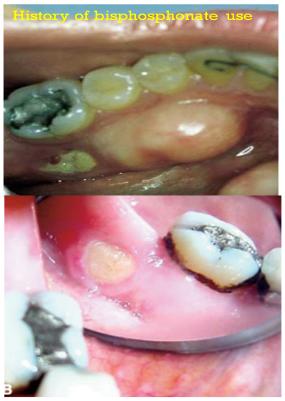
There are assumptions of a consistent, primary, causal relationship between prolonged bone exposure and use of anti-resorptive medications which should be carefully evaluated.

The incidence of prolonged non drug associated exposed bone jaw lesions , is not known, but is a prerequisite to determining MRONJ incidence.

Recent position statement by the International Task Force on Osteonecrosis of the Jaws (ITFOJ)

The ITJOF is also of the view that **bone necrosis may occur in the absence of drug therapy, with attendant oral ulceration and bone sequestration.**
.....this is uncommon but not associated with significant morbidity.
..... The incidence of OUBS is not defined in the general population.




# STUDY OBJECTIVES

- To assess the ITJOF statement that OJNAAM is not associated with significant morbidity and is uncommon.
- To determine associated clinical parameters and the incidence/prevalence of OJNAAM cases.
- To compare data from this study to published data describing MRONJ to determine similarities and differences.

# DATA COLLECTION

- We are conducting a study from primary care providers(Dentists).
- We request you to complete the questionnaire provided to you on osteonecrosis of the jaw not associated with medications.

## Appendix 4b

*We are currently conducting a survey to determine OUS prevalence/incidence. We would greatly appreciate your contribution by accessing our survey at http://bit.ly/2oddZHL. Additionally, the reference list is found at this site.* ***It is equally important to document your clinical experience, whether or not, you have seen the OUS condition.*** *We will maintain a list of contributors and to express our appreciation, we will offer a discount on the next CE program presented by the Oral Pathology/Oral Medicine Division.*

# *Oral Pathology/Oral Medicine*
## CASE CHALLENGE

EDMUND PETERS, DDS *and* VANDANA SINGH, DDS

A 55 year old woman patient presented with concerns of "Something is coming out of my gums." She first noted a sensitive area involving her right lingual mandible about a month previously and it has become progressively more painful. She was not able to identify any eliciting events. The medical history indicated management of hypertension with Coversyl Plus (perindopril and indapamide).

At clinical exam, there was a well-defined irregular ulcer (Fig. 1) involving the right lingual mandibular mucosa. The associated teeth were vital and periodontal involvement was not noted. A periapical film did not show any evidence of pathosis. Gentle manipulation of the ulcer base with a periodontal probe showed the ulcer had a hard, insensitive, somewhat mobile floor, beneath a friable white slough. The edge of the hard ulcer base was undermined and could be engaged with a spoon curette. A hard fragment was easily detached with light pressure and without local anesthesia (Fig. 2). There was minimal bleeding from the ulcer site and the patient subsequently reported relief. The patient was provided with a prescription of 0.12% chlorhexidine rinse and follow-up after 1 and 12 months showed excellent healing. Histopathologic exam of the fragment showed non-vital bone (Fig.3).

*Select the most appropriate diagnosis:*

a. Major apthous ulcer
b. Acute osteomyelitis
c. Oral ulceration with sequestration
d. Squamous cell carcinoma

*The detached fragment was comprised by a piece of necrotic bone showing extensive zones of resorption.*

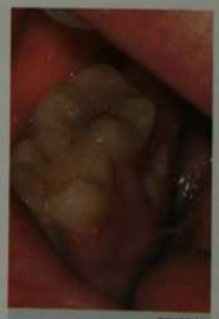


FIGURE 1

FIGURE 2

FIGURE 3