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Medication Related Osteonecrosis of Jaw – A Systematic Review

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Abstract:

Background:

Osteonecrosis, sometimes called avascular necrosis of bone, is a degenerative disorder of bone that results from a decreased blood supply. This happens because of direct tissue toxicity, which can be brought on by radiation, chemotherapy, heat damage, or smoking. Osteonecrosis of the jaw (ONJ) in labourers exposed to phosphorus fumes was referred to as "phossy jaw" in the seventeenth century. When bisphosphonates (BPs) became popular, ONJ—also known as bisphosphonate-related osteonecrosis of the jaw, or BRONJ—became more common among BP users. The American Association of Oral and Maxillofacial Surgeons (AAOMS) established a special committee to rename BRONJ as medication-related osteonecrosis of the jaw (MRONJ). Medication-related osteonecrosis of the jaws (MRONJ) is an uncommon side effect of antiresorptive or antiangiogenic drugs, such as bisphosphonates. Since its first discovery in 2003, the term has changed from "bisphosphonate-related" to "antiresorptive-related" and ultimately to MRONJ as more medications, including steroids and biologicals, have been linked to its etiology. A rare but dangerous condition that can impact a person's upper or lower jaw is medication-related osteonecrosis of the jaw (MRONJ). In the absence of prior radiation therapy, it is a progressive loss of the mandible in an individual exposed to a drug known to raise the risk of illness. It was first reported in 2002. These drugs are used to treat cancers such as multiple myeloma, as well as osteoporosis, which leads to brittle bones. Bisphosphonates are among the most used medications. Medication-related osteonecrosis of the jaw (MRONJ) includes conditions like osteonecrosis of the jaw caused by angiogenesis inhibitors, denosumab-related osteonecrosis of the jaw (DRONJ), and bisphosphonate-related osteonecrosis of the jaw (BRONJ). It is an uncommon yet incurable condition. Research has shown that MRONJ is one of the major adverse effects associated with antiresorptive medications like bisphosphonates, angiogenesis inhibitors, and denosumab, which inhibit the receptor activator of NF-kappa B ligand. The American Association of Oral and Maxillofacial Surgeons (AAOMS) defines MRONJ as the persistence of exposed necrotic bone or bone that can be probed through an intra-oral or extra-oral fistula in the maxillofacial region for more than eight weeks in patients receiving antiresorptive or anti-angiogenic agents without a history of radiation therapy or evident jaw-related metastatic disease.

Material and Methods: Major databases such as Medline were explored detailed literature search in resulting in a systematic review of medication related osteonecrosis of the jaw.

Results: Five original research scientific articles dated between 2020 – 2024 pertaining to mentioned topic were highlighted.

Conclusions: Before or during the administration of medications that could potentially lead to MRONJ, it is crucial for general dentists to deliver proactive and comprehensive dental care to effectively prevent this condition. Furthermore, oral surgeons are equipped with targeted MRONJ treatment plans tailored for every stage of the disease, ensuring the best possible outcomes for patients.

Keywords: Bisphosphonate, MRONJ, pathogenesis, risk factors, Antiresorptive agents, Denosumab, Angiogenesis inhibitors

INTRODUCTION:

Medication-related osteonecrosis of the jaws (MRONJ) is an uncommon side effect of antiresorptive or antiangiogenic drugs, such as bisphosphonates. Since its first discovery in 2003, the term has changed from "bisphosphonate-related" to "antiresorptive-related" and ultimately to MRONJ as more medications, including steroids and biologicals, have been linked to its etiology. Osteonecrosis in bone with low turnover, frequently accompanied by an initiating event like dental extraction, is a characteristic of MRONJ.

In cases of metabolic bone disease, such as osteoporosis, or to prevent skeletal-related events or hypercalcemia in advanced cancer, bisphosphonates and other antiresorptive drugs are commonly administered. Approximately 0.1% of patients receiving treatment for osteoporosis and 1% of patients receiving treatment for cancer are at risk for MRONJ; however, the rate varies greatly based on the research group and the length of exposure. Most patients are over 60, and women are impacted more frequently than men. According to a recent prospective study conducted in the UK, the incidence is projected to be 8.2-12.8 cases/million/year, and it is predicted to increase as the population ages and bisphosphonate-related medication use continues.

Epidemiology - Since the literature was evaluated in 2010, thousands of ONJ instances have been documented.10. Though 19% of this group had received pamidronate alone, 88% of the 2,408 instances were linked to intravenous therapy, mainly with zoledronate alone or zoledronate sequentially with pamidronate. Only oral bisphosphonates, primarily alendronate, have been administered to 261 patients (11%) in total. A malignancy was the underlying condition being treated in 89% of the cohort: 43% had multiple myeloma, 32% had breast cancer, 9% had prostate cancer, and 5% had other malignancies. This range most likely reflects the types of cancer that bisphosphonates are now used to treat. Osteoporosis was present in the majority of the 11% of patients who had a benign disease. Again, likely reflecting the nature of the underlying illnesses for which bisphosphonates are recommended, 61% of all patients were female. In cancer patients receiving high dosages of antiresorptive medications, osteonecrosis of the jaw (ONJ) has become a significant complication. Its importance is less evident in benign conditions like osteoporosis and Paget disease of the bone, but it nevertheless worries doctors, patients, and dentists. In 2003, ONJ was initially reported in cancer patients receiving high-dose intravenous bisphosphonates.

Determining what constituted ONJ was an early hurdle because these patients arrived with a variety of oral issues. The syndrome is characterized by exposed bone in the mouth that does not heal after appropriate intervention over a period of 6–8 weeks, according to authoritative statements from the American Society for Bone and Mineral Research and the American Association of Oral and Maxillofacial Surgeons (AAOMS). There may also be indications of osteolysis and/or osteosclerosis. Although it is widely accepted that exposed bone is a

necessary condition for ONJ, some authors diagnose ONJ in patients who do not meet this requirement but instead exhibit several nonspecific symptoms, such as sinus tract development, bone or gingival swelling, and jaw pain; 70% of these patients exhibit osteolysis, either with or without osteosclerosis, and roughly half of them go on to exhibit exposed bone. Although the progression to exposed bone indicates that some of these patients may share a clinical spectrum with classic ONJ, the inclusion of a wide range of distinct pathologies under this diagnosis is unhelpful due to the definition's expansion to include jaw pain and the recognition that the issue is not bisphosphonate-specific.

Because the bone has a limited ability to repair, treatment is challenging, and after surgery, additional deterioration may occur. The current treatments, which include oral antibiotics for known illnesses, analgesics, and antibacterial mouthwashes, are primarily supportive. Resection is saved for cases of severe illness, but debridement may be considered in situations with loose necrotic bone or obvious sequestra. Although there is mixed evidence, adjuvant treatments such as platelet-rich plasma and hyperbaric oxygen therapy have been advocated. As far as we know, there is a lack of documentation regarding the quality of life (QoL) of patients with MRONJ.

MATERIAL AND METHODS: "Osteonecrosis" AND "in jaw" AND "pathology" were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. The result was 158 articles, out of which we selected 5 articles based in the inclusion criteria. Inclusion criteria was of case studies and scientific literature between 2020-2024. Exclusion criteria was of scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of medication related to osteonecrosis of jaw following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("Osteonecrosis") AND (in jaw OR medication OR pathology OR oral OR clinical features) AND (pathogenesis)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

RESULTS:

Five articles were included in this systematic review based on the selection criteria. We analyzed and mentioned in the five articles reviewed. This included only relevant research articles and excluded articles pertaining to nonspecific search terms.

Table 1 – An overview

Author	Title	Journal	Outcome
Alberto Bedogni, Rodolfo Mauceri, Vittorio Fusco, Francesco Bertoldo, Giordana Bettini, Olga Di Fede, Antonio Lo Casto, Claudio Marchetti, Vera Panzarella, Giorgia Saia, Paolo Vescovi, Giuseppina Campisi	Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ)	Bedogni A, Mauceri R, Fusco V, Bertoldo F, Bettini G, Di Fede O, Lo Casto A, Marchetti C, Panzarella V, Saia G, Vescovi P. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Diseases. 2024 Sep;30(6):3679-709. DOI: 10.1111/odi.14887	The Expert Panel confirmed the MRONJ definition, the diagnostic work-up, the clinical-radiological staging system
Roxana Bonachea, Joseph Katz	Medication-related osteonecrosis of the jaw: A multifaceted diagnostic challenge. Mini review	Bonachea R, Katz J. Medication-related osteonecrosis of the jaw: A multifaceted diagnostic challenge. Mini review. Am J Dent. 2022 Apr 1;35(2):109-12. PMID: 35506967	MRONJ can have diverse presentations and a lengthy multisite involvement. Therefore, long-term follow up for patients with history of use of antiresorptive medications is recommended.
Shinichiro Kuroshima, Farah A Al Omari, Muneteru Sasaki, Takashi Sawase	Medication-related osteonecrosis of the jaw: A literature review and update	Kuroshima S, Al-Omari FA, Sasaki M, Sawase T. Medication-related osteonecrosis of the jaw: a literature review and update. Genesis. 2022 Sep;60(8-9):e23500. DOI: 10.1002/dvg.23500	, it was concluded that multiple factors may contribute to the development of MRONJ, although which one is the key player triggering MRONJ in the craniofacial region remains unknown.

Salvatore L Ruggiero, Thomas B Dodson, Tara Aghaloo, Eric R Carlson, Brent B Ward, Deepak Kademani	American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws-2022 Update	Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaws—2022 update. Journal of oral and maxillofacial surgery. 2022 May 1;80(5):920-43. DOI: 10.1016/j.joms.2022.02.008	This update contains revisions to diagnosis and management strategies and highlights the current research status. AAOMS maintains that it is vitally important for this information to be disseminated to other relevant healthcare professionals and organizations.
J I Aguirre, E J Castillo, D B Kimmel	Preclinical models of medication-related osteonecrosis of the jaw (MRONJ)	Aguirre JI, Castillo EJ, Kimmel DB. Preclinical models of medication-related osteonecrosis of the jaw (MRONJ). Bone. 2021 Dec 1;153:116184. DOI: 10.1016/j.bone.2021.116184	This review provides a current overview of the existing models of MRONJ, their more significant features and findings, and important instances of their application in preclinical research.

DISCUSSION:

Osteonecrosis refers to several conditions that lead to bone damage and its disruption. The causes of osteonecrosis can be different and occur in different bones in the body. Avascular osteonecrosis is associated with partial or complete loss of blood supply and most often occurs in the femur. A new type of osteonecrosis was described in 2003, and it refers to necrosis of the

jaw bone associated with the use of bisphosphonate drugs. Other types of drugs can also cause osteonecrosis besides bisphosphonates.[1]

Osteoradionecrosis is a term that refers to bone necrosis caused by radiation therapy. Radiation leads to inflammation and obliteration of the blood vessels supplying the bone, causing avascular necrosis with hypoxic, hypovascular, and hypocellular lesions. Traumatic osteonecrosis is caused by physical, chemical, or thermal bone trauma. Non-traumatic osteonecrosis is associated with infections, neoplasms, use of narcotics, and vascular causes such as ischemia, occlusion, coagulopathy, hemoglobinopathy, and some autoimmune diseases. However, some cases of idiopathic osteonecrosis that developed without an obvious etiological cause have also been described. Types of Osteonecrosis - Osteonecrosis occurring in the jaw can be divided into medication-related osteonecrosis of the jaw (MRONJ), osteoradionecrosis (ORN), traumatic osteonecrosis, non-traumatic osteonecrosis and spontaneous osteonecrosis.[2]

Medication-related osteonecrosis of the jaw (MRONJ) was first reported in 2003 and primarily involved patients receiving intravenous bisphosphonates for treatment of skeletal-related malignancies. Soon thereafter, similar cases involving oral bisphosphonates and denosumab began appearing. Although the mechanism of action of these drugs may differ, both involve osteoclast inhibition and disruption of normal bone turnover and healing.[3]

Medication related osteonecrosis of the jaws (MRONJ) is mainly due to antiresorptive or antiangiogenic drug therapy. History - Osteonecrosis of the jaws due to varied intoxications (‘‘phossy’’ jaw due to white phosphorus and radium jaw) had already been described from the 19th century. MRONJ is a major adverse event due to bone antiresorptive treatments. It was first described in 2003 as a bisphosphonate (BP) complication and has later also been shown to happen in relation with other antiresorptive drug treatments such as denosumab. Furthermore, cases of MRONJ have also been described after treatments with other medications such as antiangiogenic therapies, vascular endothelial growth factor (VEGF) inhibitors, tyrosine kinase inhibitors and tumour necrosis factor alpha (TNF-) inhibitors. It is first described as: bisphosphonate related osteonecrosis (BRONJ), bis-phossy jaw, medication related osteonecrosis of the jaws (MRONJ) and antiresorptive drug related osteonecrosis of the jaw (ARONJ).[4]

Epidemiology - MRONJ is a major adverse event of Bisphosphonate (Bp) and denosumab. The overall risk to develop MRONJ in osteoporosis patients is about 100 times smaller in comparison with cancer patients. The prevalence of MRONJ in patients with high doses of iv BP reaches about 0.348%, but is generally described under 0.005%. The overall risk for MRONJ among cancer patients exposed to zoledronic acid (ZA) or denosumab ranges between 0.7 to 6.7%. The risk is 50 to 100 times higher than cancer patients treated with placebo (0 to 0.019%).[5]

The highest risk is in patients with multiple myeloma receiving iv ZA treatment. The risk is also quite high in patients displaying unresectable aggressive benign tumour, such as giant cell tumours. The risk of developing MRONJ among osteoporotic patients exposed to oral or even iv BP or denosumab is extremely low. The prevalence of MRONJ among osteoporotic patients exposed to oral BP is comprised between 0.00038 to 0.21%. The prevalence of MRONJ among osteoporotic patients exposed to IV BP or denosumab ranges between 0.017 to 0.04%. This is almost like the risk to develop MRONJ after placebo medication that reaches 0.02%. The

duration of antiresorptive therapy is also a risk factor to develop MRONJ. The prevalence and incidence of the disease increase over time for both oral and IV antiresorptive therapies. MRONJ is more often localised at the mandible (70%) than at the maxilla (30%). [6]

MRONJ should be distinguished from other forms of osteonecrosis (ONJ) conditions and identified by history and clinical exam. The clinical criteria required to establish a diagnosis of MRONJ have remained unchanged from the previous position paper.

The case definition of MRONJ includes all the following elements:

1. Current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications.
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.
3. No history of radiation therapy to the jaws or metastatic disease to the jaws.[7]

Medications Associated with ONJ - Anti-Resorptive Agents

Bisphosphonates (BPs) are drugs typically prescribed to treat osteoporosis and cancers with metastasis to the bone. BPs share two common phosphonate groups with high affinity for calcium ions, leading them to accumulate in calcium hydroxyapatite of bone tissues with a long skeletal half-life. Under the acidic and enzyme-rich microenvironment created by active osteoclasts, accumulated BPs are released from the bone matrix to enter nearby osteoclasts, inhibiting bone resorption and accelerating osteoclast apoptosis.[8]

An association between BPs and osteonecrosis of the jaw (ONJ) was first reported in 2003. Because of its association with BP treatment, this condition was later dubbed bisphosphonate-related ONJ (BRONJ). The incidence of BRONJ in patients taking oral BPs for osteoporosis ranges from 0.01% to 0.06%, but the incidence of BRONJ in cancer patients receiving high-dose intravenous BPs is 1%–8%. Denosumab is a monoclonal antibody that targets the master regulator of osteoclast differentiation Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL).[9]

Denosumab was approved for use as an anti-resorptive agent in 2010. By preventing the binding of RANKL to its receptor, denosumab disrupts the differentiation and survival of osteoclasts, suppressing osteoclastic bone resorption. Unexpectedly, denosumab has also been associated with the development of ONJ. In addition, the incidence of denosumab-related ONJ is generally higher than that of BRONJ in patients with osteoporosis (0.283% with denosumab vs. 0.045% with BPs) and cancer (approximately 1.5 times higher in meta-analyses).[10]

Anti-Angiogenic Agents - Anti-angiogenic agents are mainly prescribed to cancer patients to restrict the tumor blood supply and suppress cancer cell migration through blood vessels. Angiogenesis is mediated by various signaling molecules, including vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β). Since VEGF is considered the master regulator of angiogenesis, VEGF and its downstream effectors are important targets for cancer treatment. Some VEGF inhibitors like bevacizumab and aflibercept bind directly to VEGF itself, while others like ramucirumab target VEGF receptor. More generic tyrosine kinase inhibitors, such as sunitinib, sorafenib, and pazopanib, can inhibit the phosphorylation and activation of receptor tyrosine kinases like the VEGF and PDGF receptors.[11]

Given that ischemia, which is caused by a restriction of blood supply to living tissues, causes tissue necrosis, it is unsurprising that anti-angiogenic drugs are also commonly associated with ONJ. MRONJ cases associated with anti-angiogenic therapy in anti-resorptive-naïve patients are rare but consistently reported. In one randomized controlled trial (RCT), bevacizumab-related ONJ appeared in roughly 0.2% of BP-naive cancer patients, compared to 0% in the placebo group. Other studies demonstrated an increased incidence of MRONJ in cancer patients treated simultaneously with BPs and anti-angiogenic reagents.[12]

Other classes of drugs associated with ONJ include the glucocorticoids, mTOR inhibitors, and various forms of chemotherapy. Although their pathogeneses in MRONJ are unclear, these drugs are commonly associated with anti-angiogenic activity. Thus, in this paper, we focus on the pathogenesis of MRONJ associated with anti-resorptive and anti-angiogenic therapies.[13]

Pathogenesis and risk factors of MRONJ - Unique characteristics of the jaw - Although BPs affect the function of osteoclasts within the skeletal system, only the jaw can suffer from osteonecrosis. The oral cavity has several unique characteristics that make it a distinctive environment. The mandible is high in calcium, which may absorb a greater quantity of BPs than the long bones. Furthermore, the long bones are produced by endochondral ossification, while the mandibles develop principally through intramembrane ossification. Human mandibles have been shown to contain more collagen than long bones.[14]

These anatomical characteristics ensure that the jaw bones are unique, with a propensity to suffer osteonecrosis. The close relationship between the teeth and jaw bone provides a route for microorganisms and other inflammatory agents to enter the bone, a situation not found in any other anatomical location. Dentoalveolar surgery is considered a major risk factor for MRONJ, especially tooth extraction. The placement of dental implants and endodontic or periodontal surgery requiring exposure and manipulation of bone are also risk factors.[15]

BPs have a greater effect on the cells of the craniofacial bones than those of the ilium and tibia. Mandibular mesenchymal stem cells have demonstrated a higher proliferation rate than long bone mesenchymal stem cells. It has been reported that the migration of dental stem cells localised near the jaw bone decreases following the administration of BPs. A recent report suggested that BPs can induce the production of reactive oxygen species, which inhibit the proliferation and migration of oral fibroblasts, thereby contributing to the pathogenesis of BRONJ. Studies found that cell proliferation, adhesion, migration, and osteogenic differentiation of periodontal ligament stem cells decreased significantly because of BRONJ lesions, a factor possibly important in the underlying mechanisms of BRONJ.[16]

Osteocyte biology - Osteocytes are the most numerous bone cell type in the adult skeleton. Osteocytes comprise 90-95% of the bone cells, while osteoclasts and osteoblasts make up the remaining 5-10%. They terminally differentiate from osteoblasts, which themselves differentiate from mesenchymal precursors residing in the bone marrow and at bone surfaces. As new bone is formed, osteoblasts synthesize osteoid at existing bone surfaces and undergo cellular transformations that involve changes in shape, size, and development of dendrite-like processes that extend into the mineralizing front of the osteoid to communicate with existing mature osteocytes. As osteoblasts differentiate into osteocytes, they become encased in their surrounding recently-mineralized bone matrix. Their cell bodies reside within lacunae, and their dendritic processes, ranging from 40–100 per cell, run through 30-300nm diameter

tunnels named canaliculi. The canaliculi traverse the mineralized bone matrix allowing intercellular communication among osteocytes.[17]

The physical structure of interconnected tunnels and lacunae is known as the osteocyte lacunar-canalicular network (LCN). The connection among osteocyte cell processes within the LCN and osteoblasts at bone surfaces is attained via gap channel junctions Gap channel junctions are formed by connexins (Cx), with Cx43 being the most abundant. Osteocytes and osteoblasts also express functional Cx43 hemichannels. Hemichannels mediate communication, not only between adjacent cells but also with the extracellular matrix as it deforms. It has been proposed that gap junctions and hemichannels contribute to maintaining bone integrity and function by permitting the exchange of bone modulators and regulating signals elicited by mechanical stimulation through influencing bone modeling and/or remodeling. Cx43 hemichannels may also play essential roles as transducers for the anti-apoptotic signals of bisphosphonates.[18]

Osteocyte Death - Osteocytes, as postmitotic cells, cannot replicate. However, they have developed adaptative mechanisms to ensure their survival under stressful conditions, such as immobilization, hypoxia, and disease. However, when their survival capacity is overwhelmed, osteocytes can die. Osteocyte death has been associated with pathological conditions including osteoarthritis, inflammatory skeletal diseases, metastatic bone disease, aging, osteonecrosis of the femoral head, osteoradionecrosis, periodontitis, and MRONJ. All three forms of cell death (apoptosis, autophagy, and necrosis) have been recognized in osteocytes. Osteocyte apoptosis was demonstrated under different conditions, including skeletal immobilization due to oxygen deprivation, osteonecrosis of the femoral head (ONFH), estrogen withdrawal, and bone microcracks after bone fatigue. It has also been associated with the natural process of aging, after menopause and bone unloading/weightlessness.[19]

Furthermore, increased osteocyte apoptosis plays an essential role in the decreased bone strength observed with glucocorticoid (GC) treatment. Notably, treatment with N-BPs reduces osteocyte apoptosis in response to fatigue loading and protects against GC-induced apoptosis by transiently increasing ERK phosphorylation. A similar effect was observed with calcitonin and mechanical stimulation. Mechanical stimulation also prevented osteocyte apoptosis, and treatment of OVX mice with a pan-caspase inhibitor inhibited OVX-induced osteocyte apoptosis and reduced bone resorption. A study showed that young mice lacking FGFR1/FGFR2 or only FGFR1 are phenotypically normal. However, at age 6-12 weeks, mice developed a high bone mass phenotype and increased porosity preceded by a striking peak in osteocyte death, particularly by apoptosis. The study identified a role for FGFR1 signaling in osteocytes and mature osteoblasts, which is required for osteocyte survival and the regulation of bone mass.[20]

Osteocytes can also undergo autophagy. GCs activate the autophagosomal pathway in osteocytes, increasing markers of autophagy. This mechanism could be beneficial to repair damaged organelles or cell membranes. However, dexamethasone also reduced the number of metabolically normal osteocytes. This effect was augmented when autophagy was suppressed, suggesting that autophagy is an adaptative mechanism used by osteocytes to attenuate the impact of GCs. The cell protective function of autophagy is likely to occur under short or moderate stress conditions. However, higher or more prolonged stress may result in an accumulation of autophagosomes and cell death. This is not surprising since autophagy

previously was suggested to act as a "double-edged sword" involved in both cell protection and cell death. Mechanical compression forces were also found to activate autophagy in osteocytic cells (MLO-Y4) *in vitro* and osteocytes *in vivo,* as demonstrated in an orthodontic tooth movement model. Notably, suppression of osteocyte autophagy caused skeletal changes similar to those caused by aging, including decreased bone mass and strength.[21]

Osteonecrosis implies the death of bone cells. It can be caused by disease or trauma, such as a fracture, which negatively affects the blood supply to the bone. Osteonecrosis can also be idiopathic, but the pathological picture and resultant early clinical course are quite stereotypical. The term osteonecrosis for certain skeletal conditions, such as aseptic, avascular, or ischemic necrosis, may be technically inaccurate, as it has not been demonstrated that the bone cells die by necrosis. Authors proposed that any form of osteocyte death, such as apoptosis or autophagy, ultimately results in secondary necrosis because dead osteocytes encased in the bone matrix cannot be immediately reached by phagocytic scavenger cells. Necrosis ultimately leads to the rupture of the osteocyte cytoplasmic membrane, with most of the intracellular content being released into the extracellular environment. [22]

Dying osteocytes release large amounts of DAMPs into the lacuna and adjacent canaliculi, including the histone deacetylase complex subunit SAP130, released and degraded cartilage matrix constituents, S100 family molecules, the high-mobility group box 1 (HMGB1) protein, purine metabolites, heat-shock proteins, and uric acid. DAMPS released into the canaliculi reach bone surfaces and vascular canals, initiating inflammatory responses by binding to various PRRs, such as the macrophage inducible C-type lectin receptor Mincle, TLR2/4, and RAGE on osteoclasts, macrophages, dendritic cells, monocytes, neutrophils. Notably, necroptosis has also been identified as a RCD form in osteocytes under certain conditions. Indeed, in addition to apoptosis, necroptosis was found in osteocytes under conditions of estrogen deficiency in OVX rats, suggesting the involvement of osteocyte necroptosis in the pathophysiology of postmenopausal osteoporosis. Furthermore, necroptotic osteocytes and trabecular bone deterioration are related to the production of TNFα in OVX ratsl. Besides apoptotic osteocytes, necroptotic osteocytes were also found in rats with GC-induced osteoporosis. Notably, necrostatin-1 (Nec-1), a specific RIPK1 inhibitor that inhibits TNF-α induced necroptosis, ameliorated the skeletal effects of GCs. The coexistence of apoptotic and necroptotic osteocytes is not surprising since it was previously suggested that apoptosis and necroptosis could co-occur. [23]

Altered balance of osteoblasts and osteoclasts - Bone remodelling is initiated by osteoclast-mediated bone resorption, in which the absorbed bone is replaced by fresh bone tissue produced by osteoblasts. BPs increase osteoclast apoptosis and other antiresorptive drugs inhibit osteoclast differentiation and function, resulting in decreased bone resorption and remodelling. The long bones contain a greater quantity of bone marrow fat than flat bones, and murine long bones contain more osteoclast precursors than jaw bones. Osteoclasts in the jaw are more sensitive to BPs than those in the long bones. If the accumulation of BPs within a bone reaches a toxic level, the BPs can affect the survival of osteoblasts and their progenitor cells.[24]

Studies showed that TGF-β1 signalling participates in MRONJ. It has an important role in bone remodelling through enhanced matrix production and osteoblast differentiation. Smad 2/3 has been identified as a downstream effector of TGF-β1. A recent study demonstrated that

treatment with BPs reduces the expression of BMP-2, which has a major role in bone remodelling, development, and osteoblast differentiation. Early differentiation marker type I collagen, intermediate differentiation markers, such as Osterix and alkaline phosphatase (ALP), and the late differentiation marker Osteocalcin has been shown to be suppressed by TGF-β1 combined with low doses of BPs in osteoblasts.[25]

Runx-2 is regulated through Smad 2/3. Furthermore, TGF-β1 is involved in the synthesis of RANKL through the reduced ability of osteoblasts to secrete RANKL, which stimulates osteoclasts via its receptor, RANK. It has been reported that the treatment of osteoblasts with BPs increases the expression of TGF-β1, resulting in reduced expression of RANKL. OPG, a soluble protein produced by osteoblasts, can inhibit the interaction between RANKL and RANK. BP treatment may alter the RANKL–OPG complex. The RANK/RANKL/OPG signalling pathway is triggered in MRONJ subjects.[26]

A recent study demonstrated that zoledronate can enhance osteoclastogenesis through elevated expression of interleukin-6 (IL-6), followed by activation of the STAT3 pathway, which is related to vessel regeneration around bone tissues, and finally the expression of RANKL. Denosumab, a recently developed antiresorptive medication, is an anti-RANKL antibody that utilises the same mechanism of action as OPG. By blocking RANKL/RANK interaction, denosumab decreases bone resorption. Using different antiresorptive mechanisms, both BPs and denosumab inhibit osteoclasts and decrease the rate of bone turnover.[27]

Given that the expression of RANKL is altered by multiple signalling pathways, the ratio of osteoblasts to osteoclasts in bone remodelling becomes altered, reducing bone resorption and turnover and giving rise to the accumulation of non-renewed and hypermineralized bone. Changes in the microenvironment of the periosteum cannot provide sufficient nutrition for the jaw, so osteonecrosis occurs following changes in the external environment. Therefore, although bone remodelling representing the pathogenesis of MRONJ may be regulated by multiple signalling pathways, the specific regulatory mechanism should be investigated further.[28]

Infection and Immunity - Infection or inflammation has long been considered a critical factor in the pathogenesis of ONJ. Bacteria have been found in biopsied specimens of necrotic bone removed from patients with ONJ. Pre-existing dental or periodontal infection in patients treated with antiresorptive or antiangiogenic medications increases the risk of MRONJ. Extraction of teeth with serious periodontal or periapical infections is a risk factor for the development of MRONJ. Another study found that periapical and periodontal infections both with and without tooth extraction can increase the risk of MRONJ because the infection is responsible for modifying the number and function of osteoclasts.[29]

Furthermore, local changes in pH caused by dentoalveolar infection or surgery are the principal factors responsible for the development of BRONJ. Therefore, inflammatory oral disease is a recognised risk factor for the development of MRONJ. Periodontal or periapical diseases are considered relevant for MRONJ. Through extensive oral health controls that prevent oral infections, the incidence of MRONJ can be significantly reduced. The proinflammatory cytokine IL-36 has been found to be present in the gingival crevicular fluid in periodontal diseases. Notably, IL-36α is highly upregulated in MRONJ lesions and has an aetiological role in the development of MRONJ. Importantly, it has been demonstrated that there is crosstalk

between the IL-36α and TGF-β signalling pathways, suggesting that infection or inflammation are key factors in the pathogenesis of MRONJ, at least in part through the TGF-β signalling pathways.[30]

The immune system is closely related to bone loss and bone regeneration. Representing innate lymphocytes, gamma delta T cells are important in bone regeneration. Such T cells are significantly reduced in osteoporotic patients who are treated with BPs, indicating that a connection exists between MRONJ and gamma delta T cell deficiency.[30] Neutrophils promote wound healing following noninfective injury. Nitrogen-containing BPs alter the defence capabilities of neutrophils and impair normal wound healing, possibly representing a critical role in the pathogenesis of MRONJ. Macrophages are sensitive to BPs, which cause an inhibitory effect and reduce the viability and differentiation capability of the macrophages. The function of macrophages is disrupted by increased MMP expression, leading to impaired wound healing in MRONJ-affected areas. Through the inhibition of RANKL, denosumab may affect the expression of RANK on immune cells, such as dendritic cells, monocytes, or macrophages.[31]

RANKL increases the production of proinflammatory cytokines and reduces monocyte apoptosis. Thus, denosumab inhibits the RANK–RANKL interaction, resulting in MRONJ, which may be related to a change in the function and survival of monocytes and macrophages. Therefore, as weak evidence, both BPs and denosumab might facilitate infection of the bone surface, resulting in an increased risk of MRONJ. Interleukins, proteins produced by immune cells, are related to the expression and regulation of the immune response, which is involved in multiple factors from lymphocytes and macrophages. It is noteworthy that IL-6 and IL-36α expression are elevated following treatment with BPs. IL-6 subsequently activates the STAT3 pathway, while IL-36α activates the ERK signalling pathway and subsequently inhibits translocation of TGF-β1 and the Smad signalling pathway. Furthermore, TLR-4-mediated macrophage polarisation participates in the pathogenesis of BRONJ in mice. Therefore, it is possible that multiple signalling pathways participate in the pathogenesis of MRONJ.[32]

Angiogenesis - Vascular endothelial growth may be a critical factor in the pathogenesis of MRONJ. Zoledronate has direct inhibitory effects on angiogenesis and vascular damage, possibly contributing to the development of MRONJ in its users, owing to reduced angiogenesis impairing healing after the intervention. The antiangiogenic effects of denosumab and zoledronate were compared, and the findings suggest that zoledronate exhibits negative effects on angiogenesis, while denosumab may not have antiangiogenic activity. Vascular endothelial growth factor (VEGF) has an essential role in angiogenesis. The antiangiogenic properties of BPs are directly linked to the pathogenesis of MRONJ, and serum VEGF levels could represent an effective early predictive marker. Monoclonal antibodies targeting VEGF receptors, as antiangiogenic drugs, are prescribed in cancer patients to prevent metastasis through the blood and lymph nodes, resulting in ischaemia and eventually MRONJ. VEGF synthesis is stimulated by TGF-β. The expression of TGF-β and angiogenesis-related signalling have been shown to be possible consequences of MRONJ. Altered VEGF expression has been observed following treatment with BPs, possibly related to the expression of TGF-β.[33]

Soft tissue toxicity - Although osteoclasts and bone are the primary targets following their exposure to BPs, it has been reported that the toxicity of BPs to soft tissue is closely related to

MRONJ. Mucosal ulcerations may be the initial pathologic event that occurs in MRONJ. BPs increase apoptosis and decrease proliferation in several cell types in vitro. In addition, the administration of zoledronic acid to oral gingival fibroblasts in vitro has been found to reduce the expression of extracellular matrix (ECM) proteins, including collagens I, II and III. It has been shown that impairment of TGF-β1 signalling is related to oral mucosal soft tissue repair in BRONJ. Increased TGF-β1 and Smad 2/3 expression are related to fibro-contractive wound healing disorders. Alterations in TGF-β1 signalling after BP treatment might explain BP-associated changes in the oral mucosal tissues of MRONJ.[34]

Other factors - Systemic diseases may increase the risk of MRONJ. BPs are occasionally administered to patients with rheumatoid arthritis to reduce bone destruction and control osteoporosis. However, BPs have been found to be associated with MRONJ in such patients, especially following their use over long durations and in high doses. Administration of zoledronate, among the most common BPs used clinically, has been shown to result in more serious MRONJ in experimental mice with rheumatoid arthritis. Therefore, rheumatoid arthritis may be a risk factor for the pathogenesis of MRONJ. Diabetes mellitus promotes inflammation and induces a change in the function of immune cells, which may affect the pathogenesis of MRONJ. It has been reported that diabetic mice are more likely to suffer from MRONJ. The relationship between diabetes mellitus and the pathogenesis of MRONJ is also related to other pathways of injury, such as microvascular ischaemia and reduced bone remodelling.[35]

Genetic factors have a moderate effect on the occurrence of MRONJ. There is an association between the presence of one or more single nucleotide polymorphisms (SNPs) and the appearance of MRONJ. The majority of SNPs are located in regions of genes associated with bone turnover or certain metabolic bone diseases. In addition, there may be germline sensitivity to BPs. Corticosteroids also increase the risk of MRONJ. Age, gender, tobacco use and type of cancer are variable risk factors for MRONJ.[36]

Role of low bone turnover - The obvious conclusion to draw from the denosumab results is that ONJ is the product of low bone turnover. Microdamage accumulation, secondary to low bone turnover, has been suggested as a contributor to the development of ONJ. A role for low bone turnover is supported by case reports documenting healing of ONJ following teriparatide treatment, suggesting that the lesions resolve when turnover is pharmacologically increased. How stimulation of bone turnover can heal ONJ is unclear, but the pivotal role of bacterial biofilms could be relevant to this. A normal response to microbial pathogens is activation of bone resorption, which is suppressed by both bisphosphonates and denosumab. The resorption of the bone surface would be expected to interfere with the laying down of a biofilm, so antiresorptives might facilitate infection by providing a stable, unresponsive surface for microbial colonization.[37]

At the doses used for treating osteoporosis, denosumab is a much more potent antiresorptive agent than alendronate, and biochemical and histological indices of bone turnover are frequently lower than those seen in cancer patients treated with high-dose zoledronate, yet ONJ frequency does not seem to be increased. Thus, low bone turnover alone does not seem adequate to produce ONJ. Even if low bone turnover is necessary for the initiation of ONJ, it is not a feature of established lesions, which show increased tracer uptake scintigraphically, increased numbers of osteoclasts histologically and bone lysis radiographically. Ongoing

studies with the novel antiresorptive agent odanacatib, an inhibitor of cathepsin K, might provide further insight into the pathogenesis of ONJ, as this agent inhibits bone resorption with much less of an effect on osteoblast activity and no known effects on the development of macrophages.[38]

Location - Around two thirds of MRONJ occurs in the mandible while the maxilla is affected in only one third of the cases with a predilection to the premolar–molar region. The predilection for the mandible is generally attributed to its limited end-arterial blood supply in addition to its higher ratio of cortical to cancellous bone. Therefore, it is not surprising that the mandible is more prone to infection, as in osteomyelitis of the jaw that also predominantly occurs in the mandible. An obvious explanation for this localization is the higher prevalence of local dental infections, namely apical and marginal periodontitis, in the respective regions. This could be attributed to the fact that root surface of molars is larger in comparison to other teeth and molars/premolars possess root furcations, which are more difficult to accessed with oral hygiene measures. It is also worth mentioning that MRONJ lesions usually originate from the alveolar process, which is frequently affected by odontogenic infections that penetrate it through root tips foramina and accessory canals or through infected periodontal tissues.[39]

Risk Factors - Numerous potential risk factors for MRONJ have been discussed. However, evidence is still sparse due to the lack of well-controlled prospective studies. Conceivable risk factors can be categorized into three groups: the type and dose of anti-resorptives or antiangiogenic drugs, systemic risk factors and local risk factors. The dosage of antiresorptive drugs is an important risk factor. The oncological dosing of intravenous bisphosphonates (e.g., zoledronate 4mg/month intravenously) and denosumab (120mg/month subcutaneously) are related to a greater risk of MRONJ when compared to dosing schemes used in osteoporosis treatment. Consequently, patients suffering from malignant diseases are more often affected with MRONJ. In these patients, additional antiangiogenic and immunosuppressive medications may further contribute to the higher MRONJ incidence.[40]

For bisphosphonates, the intravenous route of administration can be regarded as a proven risk factor compared to oral bisphosphonates. The cumulative dose, which can be determined by the duration and frequency of administration, is an additional risk factor. In a combined analysis of three prospective trials comparing the efficacy and safety of denosumab with zoledronate in treatment of metastatic bone disease, the incidence of MRONJ increased from 0.5% and 0.8% in the first year to 1.3% and 1.8% in the third year of denosumab and zoledronate intake, respectively. Co-medications and habits represent additional risk factors. Corticosteroid therapy, diabetes mellitus, chemotherapy and smoking are among the most reported potential risk factors for developing MRONJ. While a direct cause-and-effect relationship between these factors and MRONJ remains to be proven. It is remarkable that all the aforementioned factors can adversely affect the immune system and increase the susceptibility to infection. This fact may be viewed as a further support for the infection hypothesis.[41]

With respect to local risk factors, poor oral hygiene, pressure sores from ill-fitting prostheses, dental and periodontal diseases and tooth extractions are clearly linked to local infections and thus to MRONJ. A case–control study showed that periodontitis and bone loss were more common in MRONJ patients than in the controls. These results indicate that local infection could be a possible risk, or even causative, factor in the development of MRONJ. Underlying

infection can lead to extraction; this might explain the high frequency of local surgical procedures prior to the onset of the reported MRONJ cases. In a recent systematic review, tooth extraction was the preceding dental event in 61.7% of the cases. Nevertheless, it is likely that the underlying local infection, which is the typical indication for dental extraction, is the actual key factor in development of bone necrosis rather than the extraction itself. Local risk factors are of special importance as they can be influenced by the patient and by adequate preventive dental care. Of note, most of the factors as poor oral hygiene, periodontitis and tooth extraction that can lead to local infections could be prevented.[42]

Microbiology - Oral biofilm is known to harbour hundreds of bacterial species. Due to the potential causal relation of local infection in MRONJ pathogenesis, many studies aimed to investigate the microbial populations in MRONJ lesions. Several reports linked MRONJ with certain bacterial species, mainly Actinomyces. In fact, Actinomyces species are regularly found in exposed jaw bones, as in osteoradionecrosis and osteomyelitis, independent of previous antiresorptive treatment. Studies explored the relation between oral flora and MRONJ using 16S rRNA pyrosequencing techniques. In that study, anaerobic bacteria representative of periodontal microflora, mainly Porphyromonas, Lactobacillus, Tannerella, Prevotella, Actinomyces, Treponema, Streptococcus and Fusobacterium were frequently detected. Thus, it is likely that periodontitis has a great impact on the initiation of MRONJ.[43]

Furthermore, it has been shown that bisphosphonates incorporated in hydroxyapatite can increase the adhesion of different bacterial species and promote biofilm formation in vitro. Authors has evaluated the adhesion of different strains of Staphylococci and Pseudomonas to the hydroxyapatites with and without pamidronate. It was found that the adhesion of Staphylococci on the hydroxyapatite discs coated with pamidronate was seven times more than that of the uncoated discs. Moreover, the adhesion of Pseudomonas was three times more than in the controls. This means that bone loaded with bisphosphonates is more susceptible to infection not only because of the suppression of defense mechanisms, especially osteoclast activity and bone remodeling, but also because bone loaded with bisphosphonates is more prone to bacterial colonization.[44]

Medication Related Osteonecrosis in Other Locations - Osteonecrosis lesions do not exclusively occur in the jaw bones. Several recent publications confirmed the occurrence of osteonecrosis of the ear canal in patients receiving antiresorptive drugs. An infectious genesis has been also discussed regarding these cases as minor trauma to the thin integumental layer that covers the bone and bacterial contamination could lead to an infection resulting in osteonecrosis.[45]

Reduced Bone Formation Vs Reduced Bone Resorption Caused by Anti-Resorptive Agents - The most popular hypothesis regarding the pathogenesis of MRONJ points to excessive suppression of bone remodelling induced by anti-resorptive agents. Anti-resorptive agents, such as BPs and denosumab, inhibit both osteoclastic bone resorption and osteoblastic bone formation due to osteoblast–osteoclast coupling. Anti-resorptive agents reduce the release of osteogenic clastokines by inhibiting osteoclast differentiation; they reduce the release of osteogenic growth factors embedded in the bone matrix by decreasing bone resorption. Therefore, suppression of bone remodelling reduces both bone resorption and formation. This

raises the question of whether anti-resorptive agents cause ONJ by suppressing bone resorption or formation.[46]

The remodelling suppression hypothesis follows the idea that anti-resorptive agents suppress bone remodelling to a greater extent in the alveolar process than the basal bone due to its higher rate of bone remodelling. Both the rates of bone formation and resorption are higher in the alveolar process, probably to meet the functional demands of mastication. Treatment with anti-resorptive agents should simultaneously affect both bone formation and resorption, so this phenomenon does not conclusively address the question.[47]

Another line of evidence used to support the reduced bone formation hypothesis comes from the therapeutic effect of teriparatide in MRONJ patients. Teriparatide, which comprises the initial 34 amino acids of parathyroid hormone, promotes osteoblast-mediated bone formation. Authors demonstrated that patients treated with teriparatide showed increased MRONJ lesion resolution and improved serum levels of bone formation markers compared to patients treated with a placebo. However, teriparatide increases bone formation and resorption markers in both BP-naive and BP-pretreated patients, probably because of osteoblast–osteoclast coupling. Moreover, increased bone resorption markers in MRONJ patients treated with teriparatide. Thus, the therapeutic efficacy of teriparatide cannot resolve whether MRONJ arises because of reduced bone formation or resorption.[48]

Romosozumab is a monoclonal antibody against sclerostin that has bone anabolic and anti-resorptive effects and that was approved by FDA in 2019 for use in treating postmenopausal osteoporosis. If MRONJ is caused by reduced bone formation, romosozumab should theoretically reduce ONJ incidence. Although one rat study reported no incidence of ONJ after the administration of clinically relevant doses of romosozumab, rodents normally require much higher doses of anti-resorptive agents to see MRONJ in studies with a limited number of animals. Additionally, an analysis of FDA's Adverse Event Reporting System (FAERS) found that romosozumab treatment was associated with a slight but significant increase in the risk of MRONJ. These findings suggest that ONJ associated with anti-resorptive agent treatment is likely caused by reduced bone resorption rather than reduced bone formation.[49]

Reduced Bone Resorption Versus Reduced Angiogenesis - Although MRONJ has a complex etiology, the link between anti-resorptive and anti-angiogenic agents and ONJ implicates reduced bone resorption and/or angiogenesis. This suggests three possible scenarios: Reduced bone resorption and angiogenesis are independently associated with MRONJ (Model 1); reduced angiogenesis leads to reduced bone resorption, resulting in MRONJ (Model 2); and reduced bone resorption leads to reduced angiogenesis, resulting in MRONJ (Model 3). Significant evidence links bone resorption and angiogenesis. First, treatment of cancer patients with zoledronic acid induces a significant reduction of circulating angiogenic factors, such as VEGF, PDGF, and TGF-β. [50]

Animal model experiments demonstrated reduced neo-vessel formation in the BRONJ group. Denosumab significantly inhibited angiogenesis in cancer patients and the denosumab mimic OPG-Fc significantly reduced periodontal vascularity in mice. Although studies suggested denosumab has no anti-angiogenic activity several factors suggest this is a misinterpretation of their results. First, they used a mouse model even though denosumab does not affect murine RANKL. Second, the human umbilical vein endothelial cells (HUVECs) used in their in vitro

experiments were inappropriate because of their low levels of RANKL transcript and because of conflicting reports regarding the role of RANKL in HUVECs. Moreover, any anti-angiogenic activity of denosumab can only be properly assessed in vivo, as the major source of RANKL is bone tissue.[51]

In contrast, angiogenic factors like VEGF, PDGF, and FGF-2 directly stimulate osteoclast differentiation and function in vitro and in vivo. Furthermore, VEGF inactivation by genetic deletion or pharmacologic inhibition suppresses osteoclastic bone resorption in vivo Together, these data demonstrate a close association between bone resorption and angiogenesis, excluding Model 1. Considering its low incidence and dose-dependency, MRONJ seems to occur only when angiogenesis and/or bone resorption are severely disrupted. Anti-angiogenic agents, such as sunitinib and sorafenib, reduced serum and urine levels of the bone resorption marker N-terminal telopeptide (NTx) in cancer patients by roughly 40% but this effect was much less pronounced than the effect of low-dose BPs in patients with osteoporosis. Given that MRONJ occurs in less than 0.1% of BP-treated patients with osteoporosis, moderate reduction in bone resorption cannot explain the incidence of anti-angiogenic agent-related ONJ. Moreover, while the simultaneous use of anti-resorptive and anti-angiogenic agents increased the incidence of MRONJ, the combination of zoledronic acid and bevacizumab did not significantly alter serum levels of the bone resorption marker serum C-terminal telopeptide compared to zoledronic acid alone. Together, these findings exclude Model 2. [52]

Anti-resorptive therapies with BPs or denosumab significantly reduced circulating angiogenic factors and vascularity in cancer patients, but this was less effective than bevacizumab in terms of reducing circulating free VEGF. However, in humans, circulating VEGF levels are much lower than local tissue VEGF levels. Moreover, local VEGF levels during wound healing typically rise several-fold above circulating VEGF levels. This means the reduction in local VEGF levels observed in response to zoledronic acid was likely more dramatic than it seemed. In addition, while bevacizumab barely affected the levels of angiogenic factors like PDGF and FGF-2, zoledronic acid significantly reduced circulating levels of VEGF, PDGF, and FGF-2. Furthermore, anti-resorptive and anti-angiogenic agents synergistically improved cancer patient survival at least partly, because both have anti-angiogenic effects. Therefore, these findings indicate that Model 3 is the most promising scenario. In it, anti-resorption therapy causes ischemic ONJ by suppressing local angiogenesis. Because the basic multicellular unit responsible for bone remodeling comprises osteoclasts, osteoblasts, and microvessels, it is reasonable to expect a physiological coupling of bone resorption and angiogenesis. [53]

Source of VEGF During the Healing of Extraction Sockets - Traumatic surgeries like tooth extraction are the strongest local risk factor for the development of MRONJ. After tooth extraction, acute inflammation occurs, followed by angiogenesis and the migration of mesenchymal stem cells. Accordingly, local VEGF levels rise significantly after tooth extraction, and disturbance of VEGF can delay the healing of extraction sockets. These findings suggest that local elevation of VEGF in tooth extraction sockets is critical for normal healing. [54]

Several lines of evidence suggest osteoblast-derived, bone-matrix-bound VEGF is the primary source of local VEGF during extraction socket healing. First, deletion of *Vegfa* in osteoblast lineage cells greatly reduced VEGF production at a site of bone repair in mice. VEGF was

detected in osteoblasts rather than osteocytes in normal bone tissue and in a site of bone repair. Moreover, VEGF from early osteolineage cells, but not mature osteoblasts/osteocytes, plays a crucial role in angiogenesis and bone formation during fracture repair. This suggests osteoblasts and their precursor cells are an important source of VEGF in bone healing. [55]

Second, the most prominent matrix-bound isoforms of VEGF have strong pro-angiogenic activity. Several isoforms of VEGFA arise from alternative mRNA splicing, and the most abundant isoforms include VEGF189, VEGF165, and VEGF121. VEGF189 and VEGF165 are matrix-bound because they have a heparin-binding domain that allows interaction with the extracellular matrix, whereas VEGF121 is diffusible because it lacks the heparin-binding domain. Matrix-bound VEGF189 and VEGF165 have strong pro-angiogenic activity, but VEGF121 has anti-angiogenic or weak pro-angiogenic activity. Therefore, the pro-angiogenic VEGFs produced in the extraction socket are likely matrix-bound VEGFs. [56]

Last, zoledronic acid reduces circulating VEGF levels even 21 days after treatment. Zoledronic acid accumulates primarily in the bone matrix, with its plasma concentration decreasing to 1% or less of its peak level by 24 h after infusion. This means the concentration of zoledronic acid in other tissues is negligible compared to bone. Therefore, long-lasting reductions in circulating VEGF are likely due to the reduced release of matrix-bound VEGF from bone where zoledronic acid remains active. It is possible, however, that zoledronic acid also inhibits the production of VEGF from osteoblasts via osteoblast–osteoclast coupling. Together, these data indicate that the source of VEGF during the healing of extraction sockets is likely osteoblast-derived, bone-matrix-bound VEGF. [57]

Reduced Angiogenesis Aggravates Bacterial Infection-Induced Bone Necrosis - The unique occurrence of MRONJ in the oral cavity is largely attributed to the fact that an extraction socket is an open wound, inviting infection by one or more of the approximately 700 species of oral bacteria. The risk of MRONJ increases when patients with periodontal disease undergo tooth extraction, suggesting oral bacterial infections contribute to MRONJ pathology. Exposed bone in the extraction socket is particularly vulnerable to bacterial infection when patients take anti-resorptive or anti-angiogenic agents. This is because local vascularization is crucial for bacterial clearance after tooth extraction. Damaged tissues and bacterial contamination in the extraction socket trigger the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. These mediators promote vasodilation and increase vascular permeability, allowing immune cells to migrate to the site of injury from circulation. Neutrophils are the first immune cells to arrive at the site, followed by macrophages and lymphocytes. They perform phagocytosis to engulf bacteria and necrotic tissue debris and release antimicrobial substances and enzymes to further combat infection. [58]

When local vascularization is reduced by anti-resorptive or anti-angiogenic agents, however, the initial recruitment of these immune cells and bacterial clearance are compromised. Additionally, reduced local vascularization leads to hypoxia, creating a favorable environment for the anaerobic bacteria that comprise the majority of species in MRONJ sites. Hypoxia also impairs the function of recruited immune cells by reducing their survival, phagocytic activity, and production of reactive oxygen species. Together, the reduced angiogenesis secondary to treatment with anti-resorptive or anti-angiogenic agents aggravates bacterial infections in extraction sockets, leading to severe chronic inflammation. [59]

Osteocyte death in MRONJ - Though bone necrosis is the hallmark of MRONJ, little attention has been paid to investigating the type of cell death afflicting osteocytes in MRONJ. Early studies found focal areas of bone matrix necrosis in the mandible of dogs treated for three years with ALN. It has been shown that osteocyte death occurs as a physiologic end-stage of the skeleton's life cycle, and that the prevalence of osteocyte death increases with skeletal aging. Investigators might assume from these findings that a systematic process for removing dead osteocytes, perhaps based on bone resorption, exists in the adult skeleton. Based on these ideas, the authors suggested that jaw bone necrosis associated with ALN treatment resulted from dead osteocyte accumulation caused by the suppression of bone resorption by ALN. In contrast, it was suggested that the necrotic alveolar bone would have been efficiently removed in the absence of an N-BP and a normal bone turnover rate, particularly in jawbones that appear to have higher basal bone turnover than the postcranial skeleton. These authors also proposed an alternate theory in which ALN could have directly affected osteocyte viability, decreased their life span and increased the rate of bone necrosis. [60]

Clinical and preclinical data indicate that for MRONJ to occur, systemic risk factors (e.g., pARs and AgIs) and oral risk factors, such as tooth extraction and inflammatory dental disease (e.g., periodontitis, periapical infection) must co-occur. Oral risk factors associated with inflammation and/or infection induce local production of pro-inflammatory cytokines, such as TNF-α and IL-1, which stimulate inflammation and osteocyte death in alveolar bone. Cell death associated with tissue infection and inflammation is linked to ACD. However, as described earlier, strong evidence suggests that biomolecules that activate inflammation, like TNF-α and others, simultaneously activate cell death by RCD mechanisms, including necroptosis and apoptosis, and stimulate inflammation. In cells that die by apoptosis, the apoptotic cell bodies are quickly taken up by neighbouring cells and degraded within phagolysosomes. Therefore, and in contrast to necrosis, apoptosis might not induce an inflammatory reaction harmful to the host. [61]

As seen in necrosis, necroptotic cells also manifest loss of membrane integrity and release of the cellular content, which function as DAMPs. Recently, Mincle was recognized as the PRR that more specifically senses another DAMP, SAP-130. Dying osteocytes release SAP-130, and Mincle is highly expressed at skeletal sites of osteocyte death. Mincle is specifically upregulated in osteoclasts in a RANK-RANKL-independent fashion, and its signaling appears to target bone resorption upon osteocyte death. In patients taking N-BPs, though bone resorption is inhibited, the number of osteoclasts at bone surfaces does not decline. When necrotic bone persists due to the inhibition of bone resorption by pARs, DAMPs, including SAP-130, would accumulate in the necrotic alveolar bone, suggesting that Mincle expression in N-BP-treated patients would be chronically elevated. Indeed, Mincle is highly expressed in necrotic bone areas of patients with MRONJ, and these authors suggested that SAP-130 and Mincle could be potential early markers for MRONJ. The DAMP molecule HMGB-1 activates TLR-2 and TLR-4, triggering an immune system response and inflammation in the extracellular milieu. The pathophysiological significance of elevated expression of DAMPs and PRRs in the context of impaired bone resorption, as occurs in pAR-treated patients, has not been directly investigated. [62]

The Mucosal Immune Response and MRONJ - The mucosal immune system defences against a variety of microbes and maintains the immune homeostasis in the oral cavity under healthy conditions. It has a sophisticated anatomical structure, several indigenous microorganisms, and immune cells. A tightly interlaced cell-to-cell network of epithelial cells acts as a physical barrier, thereby defending external stimuli and balancing the intricate interaction between the host and exterior environment. Furthermore, several indigenous microorganisms act as a biological barrier to prevent pathogen colonization. Moreover, various immune cells and secreted inflammatory cytokines play an important role in immune surveillance and homeostasis. Unfortunately, BPs and risk factors that impact the mucosal immune system, coupled with bacterial infection contribute to the development of MRONJ.[63]

The Destruction of Mucosal Barrier Protection - There are hundreds of thousands of bacterial species in the oral cavity. An imbalanced bacterial flora can contribute to multiple mucosal diseases. Colonization of unique bacterial communities, coupled with a dysfunctional innate immunity, has been shown to affect the pathogenesis of ONJ. Indigenous microbiota, as biological barriers, are antagonistic bacteria, which suppress the invasion and colonization of harmful microorganisms. Several protective mechanisms of indigenous microbiota have been reported, including competition for nutrients, direct killing, and enhancement of immune responses. In a previous report, it was demonstrated that BPs exerted inhibitory effects on the growth of select bacterial species.[64]

Recent, studies demonstrated increased local bacterial infiltration in MRONJ mice. Moreover, after extracting healthy teeth from mice, and following with zoledronate infusions, no differences were observed in the formation of osteonecrosis between mice receiving broad-spectrum antibiotic treatment and negative controls. Interestingly, antibiotic-mediated oral dysbiosis causes increased bone necrosis when extracting teeth with ligature-induced periodontitis. Moreover, they showed that broad-spectrum antibiotic treatment suppressed the normal flora to protect against inflammation-induced osteonecrosis by dampening the formation of osteonecrosis and by activating osteoclasts. The results showed that the imbalance in oral flora may be a prerequisite for MRONJ and biological barriers are of great necessity to prevent the occurrence of MRONJ. Clinical data also supported the view by the evidence that about half of individuals diagnosed with MRONJ are multiple myeloma (MM) patients, who mostly underwent antibiotics treatment for a long time. Although antibiotic treatment has been shown to be effective for MRONJ, increased attention should be paid to patients receiving long-term antibiotics treatment. [65]

Different from the intestinal mucosal barrier, the specific structure of the dento-gingival junction makes the oral mucosal barrier more fragile. The bone-invasion dental measurement and mechanical trauma disrupt the integrity of the oral mucosal epithelial barrier and thus facilitate bacterial invasion and colonization, resulting in jawbone infection. Additionally, mucosal ulceration and periodontal diseases can have a destructive effect on the oral mucosal barrier, and mucosal ulceration is believed to be the initial pathologic event of ONJ. BPs have a direct toxic effect on soft tissue.66 Keratinocytes and fibroblasts are two of the most important compartments in the mucosal barrier. Previous reports have shown that BPs can induce senescence of human oral keratinocytes and suppress the cell viability and migration of keratinocytes and fibroblasts. Furthermore, high levels of bisphosphonates can cause apoptosis

and necrosis. Therefore, disruption of the oral mucosal barrier is not only induced by potential risk factors but also by the toxic effect of BPs on soft tissue.[66]

The Osteo Immune Response and MRONJ - Bone is dynamic tissue undergoing continuous remodeling and repair to maintain bone homeostasis. Bone remodeling is a process, which is related to osteoblasts-mediated osteogenesis and osteoclasts-mediated osteoclastogenesis. During the healthy state, bone resorption and bone formation take place at equal rates to ensure an adequate quantity of bone mass and a healthy functional status. However, inflammatory diseases are always accompanied by bone loss in the oral cavity, such as periodontitis. Under the inflammatory condition, the immune system not only protects against the invasive pathogens and reduces inflammation, but also maintains the bone homeostasis by removing the damaged and apoptotic tissue and stimulating the bone tissue repair and regeneration, which fostered a novel interdisciplinary field, "osteoimmunology". Moreover, many regulatory molecules are shared by the immune and skeletal system, including cytokines, receptors, signaling molecules, and transcription factors. Additionally, decades of reports have identified that immune cells participate and mediate skeletal homeostasis by releasing multiple types of cytokines. [67]

Osteal macrophages were reported to locate adjacent to osteoblasts and regulate bone formation, playing diverse roles in skeletal homeostasis. However, BPs affect the process of immune and bone interaction, thereby leading to the imbalance of bone homeostasis and low bone turnover. The low bone turnover promotes the accumulation of microdamage in the jaw bone and the opportunity of bacterial colonization, being suggested as a contributor to the development of MRONJ. Therefore, understanding the role of BPs-altered osteo response in the process of bone remodeling is critical to our exploration of the pathogenesis of MRONJ. [68]

Imaging modalities (orthopantomography/CT/MRI)

The panoramic examination provides an overall view to examine the whole mandible and maxilla. It can be an unexplained bone loss not attributed to periodontal inflammation with a change in trabecular bone pattern. Radiographic features can manifest in the early stage through orthopantomography as diffuse sclerotic bone, ill-defined radiolucency, or a mix of a radiopaque and radiolucent lesion in addition to a nonhealing extraction socket. In advanced stages, the radiographic presentation of MRONJ may mimic the classic appearance of chronic osteomyelitis as sequestrum formation, thickening of lamina dura, and pathological fractures. For a more detailed examination, digital imaging as in CT and cone-beam CT (CBCT) provide high-quality tomographic images to reveal MRONJ/ARONJ lesions. Diffuse osteosclerosis, bone resorption, degenerated cortical bone, periosteal reaction, and bone fistulas are findings that reveal the spread and the extent of such a lesion.[69]

CBCT is superior to CT since it exhibits a higher resolution in the alveolar bone and the jawbones. MRI scans are less precise in skeletal imaging than CT scans. Hence, the appearance of ONJ on MRI is variable and unpredictable. The MRI diagnostic modality depends mainly on the signal intensity alteration on the bone and adjacent soft tissues. Studies showed varied signal intensity on T1 and T2, which were believed to be stage-related changes. The T1-weighted image showed reduced signal intensity. The T2-weighted image showed increased signal intensity in the early stage of the disease and increased or decreased signal intensity in

advanced stages of the disease. This variability in the T2-weighted image was believed to be due to the nature of the wound and the stage of the disease.[70]

The diagnostic value of MRI in ONJ not well established. However, the main advantage of MRI over other imaging modalities is the ability to assess the degree of extent of the lesion in bone and soft tissues, which helps in planning for surgical debridement and resection. Diffusion-weighted imaging (DWI) is utilized for treatment response forecasting. DWI is used in monitoring and predicting recurrence of highly recurrent lesions. Because of its short processing time, it could be used along with an MRI protocol. A newly introduced modality called bone scintigraphy provides less information about anatomical configuration than the CT or MRI. For MRONJ patients, single-photon emission computed tomography (SPECT) has been used for localization of physiological changes in the bone. It can be used to assess the activity of the surrounding bone. Despite the advantage of this modality, it appears to be sensitive but not specific.[71]

MEDICAL MANAGEMENT - Treatment of MRONJ with medical therapy alone is most employed for patients with less severe disease, those who decline surgery, or those whose comorbidities preclude them from surgery. Medical therapies currently in use include topical, oral and intravenous antimicrobials, other medications and hyperbaric oxygen (HBO).

Antimicrobials - Topical antimicrobials

Chlorhexidine gluconate 0.12% is a topical bactericidal and bacteriostatic agent that has been shown to be effective in treatment of patients with MRONJ. Although the pathogenesis of MRONJ remains unclear, there is evidence that the oral flora, and more specifically biofilms, contribute to the disease process. The use of chlorhexidine is thus rationalized by its ability to decrease total bacterial counts, including potentially pathologic organisms. Advantages of chlorhexidine include low cost, ease of use, availability, patient acceptance, and efficacy. Disadvantages include patient intolerance, lack of compliance associated with long-term use, dental staining, and opportunistic infection, as well as alterations in taste. In our practice, we commonly recommend chlorhexidine for management of stage 1 disease as a singular therapy. For more advanced stages, we routinely recommend chlorhexidine in addition to other medical and surgical therapies.[72]

Oral antimicrobials - Antimicrobials are a mainstay in the management of MRONJ. Antimicrobial therapy is based on clinical observation and scientific literature suggesting that pathogenic bacteria may contribute to MRONJ. The precise organism(s) responsible remain to be identified but it seems that most infections are polymicrobial. Systemic antibiotics may decrease bacterial counts in the oral cavity, including pathogenic organisms. Selection of specific antibiotics should be based on patient tolerance, compliance, and prior antibiotic exposure. One should also consider therapies targeted against common colonizers of MRONJ lesions, including Actinobacteria, Firmicutes, Fusobacteria, and Bacteroidetes. Members of these phyla include aerobic and anaerobic organisms commonly susceptible to penicillin; therefore, penicillin remains our first antibiotic choice. Our most common penicillin alternates are clindamycin, fluoroquinolones, and/or metronidazole. Although there are no data to clarify the most appropriate duration of antibiotic therapy for MRONJ, we generally prescribe a 2-week course for patients with persistent stage 1 disease and up to a 4- to 6-week course for more severe cases. [73]

Intravenous antimicrobials - Intravenous antimicrobials may be of benefit in patients with pathogenic organisms resistant to oral agents and may provide greater tissue penetration in certain cases. However, there have been no satisfactory trials demonstrating greater efficacy of intravenous agents compared with oral medications in management of MRONJ. When all available oral agents have been exhausted and no less invasive option exists, it is our practice to employ long-term (6 weeks) intravenous antimicrobials. In the future, it is conceivable that antimicrobial therapy may be more effective in MRONJ treatment when combined with developing delivery mechanisms most capable of penetrating biofilms.[74]

Other Medications - Pentoxifylline and vitamin E

The combination of pentoxifylline and vitamin E has been used successfully in the treatment of jaw osteoradionecrosis and MRONJ; however, the specific mechanism of action in MRONJ remains unclear. Pentoxifylline (Trental), a xanthine derivative with an excellent safety profile, is used primarily for the treatment of intermittent claudication and other symptoms of peripheral vascular disease. It has been shown to decrease inflammation and reduce blood viscosity by increasing erythrocyte deformability. Vitamin E decreases tissue inflammation and fibrosis, and is a scavenger of free radicals capable of cellular injury. Alpha tocopherol is the most active form of vitamin E in humans, and is widely available, well-tolerated, and readily absorbed. Numerous reports supporting the role of both inflammation and decreased vascularity as contributors to MRONJ make the use of this relatively well tolerated drug combination a rational choice. The duration of treatment has not been clarified, but borrowing from the osteoradionecrosis literature benefits may plateau after 2 to 3 years of use. Our group typically offers this therapy to any patient regardless of disease stage. The recommended dose of pentoxifylline is 400 mg sustained release twice daily and 1000 IU vitamin E daily. Reasons for termination of therapy include patient intolerance, disease resolution, or after 36 months. However, because treatment duration remains empiric continued administration should be determined by the patient, treating physician, and medical team. In addition, we routinely maintain these medications perioperatively in those who require surgical treatment of the MRONJ.[75]

Hyperbaric Oxygen Therapy - HBO therapy has been used for management of osteoradionecrosis of the jaw for many years of MRONJ. Those advocating HBO for treatment of MRONJ argue that HBO provides greater oxygen to tissues with impaired vascularization. Additionally, HBO reverses impaired leukocyte function and also supplies reactive oxygen and nitrogen species. All of these effects theoretically contribute to improved wound healing and bone turnover. HBO is seldom used as a singular treatment modality, but is more commonly used as a surgical adjunct. HBO therapy is a controversial, costly, and time-intensive treatment whose efficacy deserves further study. [76]

SURGICAL MANAGEMENT Our focus in the surgical treatment of MRONJ is directed toward stage-specific therapeutic options. Patients with stage 0 and stage 1 disease generally do not warrant surgical intervention, but benefit from medical management, as outlined elsewhere in this article. In our practice, surgical treatment is offered when disease progresses to the point where symptoms are not controlled with medical therapies. Regardless of disease stage any overtly mobile necrotic bony sequestra should always be removed. A wide spectrum of disease is often seen with stage 2 MRONJ, ranging from focal minimally symptomatic

exposed bone to severely painful widespread bone necrosis. It is thus difficult to recommend a single surgical treatment approach in these patients. Rather, the decision regarding operative intervention depends on the patient's medical status, comorbidities, pain level, their treatment goals, and the extent of disease. Those with mild stage 2 disease who have minimal pain and localized bone exposure may not require surgical intervention and may remain stable with medical management. Several surgical treatment modalities, all with varying success rates, have been described for patients with symptomatic stage 2 MRONJ. Debridement and marginal and segmental resection are terms commonly seen in the literature describing surgical treatment of MRONJ. Debridement and marginal resection both refer to removal of necrotic bone, primarily in the alveolus, with the goal of maintaining an intact inferior border of the mandible. Segmental resection, on the other hand, refers to en bloc removal of involved bone, including the inferior border of the mandible, with a resulting continuity defect. Success rates vary widely in response to local debridement/marginal resection ranging from 15% to 100%. [77]

Higher success rates have been found when debridement was combined with multilayer primary soft tissue closure and failure to achieve adequate soft tissue closure has been thought to affect surgical outcomes adversely. Success of debridement or marginal resection may also be limited by the difficulty in differentiating healthy from diseased bone. Inadequate removal of affected bone has been found to increase MRONJ recurrence. Because the extent of the osteonecrosis is often greater than what is seen clinically, preoperative imaging with CT or cone beam CT, bone scintigraphy, and/or MRI can also aid in determining the type and extent of surgery and assist in identifying bony margins. Intraoperative fluorescence-guided debridement has been suggested to assist in differentiating necrotic from viable bone. [78]

Tetracycline is used as a bone label for this purpose because it is incorporated into sites of bone remodeling and thus will only be seen in viable bone. The technique involves preoperative administration of doxycycline (100 mg twice a day 10 days before surgery). A fluorescent light source is applied to the affected region during debridement and areas of necrotic bone are seen to fluoresce as a pale bluish-white color whereas viable bone appears brightly fluorescent. Autofluorescence (using the fluorescent lamp without preoperative administration of doxycycline) has also been reported to aid with the identification of viable bone. During surgical debridement, extraction of any involved teeth is also indicated. It is better to debride diseased tissue adequately, including removing adjacent potentially involved teeth, than it is to leave the area inadequately treated to preserve teeth. Any sharp bony spicules should be removed and extraction sockets and bony margins should be free of sharp edges to aid in achieving tension-free primary closure. All resected hard and soft tissue should be sent for histopathologic examination as well as culture and sensitivities to allow directed postoperative antibiotic therapy. [79]

Adjunctive treatments, including autologous platelet-rich plasma and low-level laser therapy, have been used in conjunction with surgical debridement to improve postoperative healing. The data are inconclusive as to the added value of these modalities. A systematic review of the literature on autologous platelet concentrates concluded that, although the evidence was weak, the addition of platelet concentrates improved healing outcomes after surgical debridement of osteonecrosis. Low-level laser therapy, purported to stimulate bone healing by increasing vascularity and osteoblastic differentiation, has been used in conjunction with surgical

debridement of osteonecrosis. However, rates of healing after surgical debridement with and without low-level laser therapy are comparable and further research is needed to determine the value of low-level laser therapy. [80]

In summary, in cases of stage 2 MRONJ when debridement and marginal resection is determined to be the indicated, treatment the following principles should be applied:

1. Appropriate preoperative imaging to assess the extent of disease,
2. Removal of all necrotic bone and any involved teeth to achieve disease-free bony margins,
3. Removal of any sharp bony edges and spicules,
4. Achievement of a layered tension-free primary wound closure whenever possible,
5. Culture-directed postoperative antibiotic therapy until mucosal healing is seen, and
6. Restraint from wearing any oral prosthetic devices until complete mucosal healing is seen.[81]

Patients with stage 3 MRONJ who present with extensive maxillofacial involvement may benefit from wide local debridement or segmental resection of necrotic bone. We reserve this treatment for those with severe symptomatic disease when other modalities have failed. Segmental resection for treatment of stage 3 osteonecrosis of the jaw has shown generally favorable outcomes with up to a 90% success rate. As with stage 2 disease, evidence of osteomyelitis at one of the resected margins is a predictor for recurrent disease. Our experience with segmental resection in cases involving both the maxilla and mandible has overall been positive with successful longterm resolution of MRONJ without recurrence. The same treatment principles outlined for stage 2 MRONJ also apply to patients with stage 3 disease. [82]

Mandibular Resection - The CT scan is also used to determine the extent of disease with a view toward identifying margins of viable bone. Depending on the patient's medical status, reconstruction may be limited to the osteosynthesis plate or may include microsurgical free tissue transfer. Double-layer primary closure of the wound margins is achieved, including primary closure of extraction sites in the surgical area. When reconstruction involves only the osteosynthesis plate we approach this transorally and have found we can perform a hemimandibulectomy with this method.

Maxilla Resection - The same principles apply for treatment of stage 3 MRONJ involving the maxilla. All loose necrotic bone sequestra are removed and the area thoroughly debrided and when possible primary wound closure is performed. CT is important to help delineate the extent of bony involvement. [83]

CONCLUSION:

The mechanism of ONJ, a multifactorial condition in patients receiving systemic antiresorptive medication for osteoporosis or primary or metastatic bone cancer, is yet unknown. Research on humans and animals suggests several processes that work together to accelerate the onset and severity of the illness. The core of the illness process is histologic bone necrosis. There is substantial evidence that antiresorptive, trauma, and/or inflammation/infection are important variables that are both required and sufficient for the formation of ONJ. Bone necrosis can happen when antiresorptives are used in conjunction with trauma, such as tooth extractions, or inflammation or infection from periodontal or periapical diseases. Clinical ONJ, or loss of soft tissue integrity, can result from necrotic bone. The illness is further complicated by surgical intervention, which also directly disrupts the soft tissues. Only trauma or infection has been

linked to case reports of exposed, necrotic bone with loss of soft tissue integrity. In a positive feedback loop, bone exposure spreads infection and inflammation, intensifying or broadening the condition. The cycle continues as more soft tissue integrity is lost, which results in ongoing bone necrosis.

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