Review

Understanding Jaw Osteonecrosis: Avascular, Bisphosphonate-Related, and Osteoradionecrosis Explained

Lara Bouakel *

Posted Date: 9 May 2025

doi: 10.20944/preprints202505.0680.v1

Keywords: Avascular osteonecrosis; Medication-related jaw osteonecrosis; Osteoradionecrosis

 doi:10.20944/preprints202505.0680.v1

Review

Understanding Jaw Osteonecrosis—Avascular, Bisphosphonate-Related, and Osteoradionecrosis Explained: Narrative Review

Lara Bouakel

Independent Researcher; bouakellara@gmail.com

Abstract: Objective: This narrative review synthesizes current knowledge on medication-related osteonecrosis of the jaw (MRONJ), osteoradionecrosis (ORN) and the newly emerging avascular osteonecrosis of the jawbone due to corticosteroid use. It explores their aetiopathogenesis and clinical features. Additional comparative analysis of these conditions was made to highlight their distinct and overlapping characteristics, aiding in their better understanding and differentiation. **Materials and Methods:** A comprehensive literature search was conducted using PubMed and Scopus with a restriction on the publication date, accepting those published between 2010 and 2025. The search included keywords such as "avascular jaw osteonecrosis", "medication-related osteonecrosis of the jaw" and "osteoradionecrosis". Articles were selected based on relevance, focusing on clinical studies, systematic reviews, and emerging knowledge on the subject. **Results:** Despite differences in their pathogenesis, avascular osteonecrosis of the jaw due to corticosteroid use, MRONJ, and ORN exhibit similar clinical manifestations, including bone exposure, pain, and infection. Despite their similarities, attention should be given to fully understand their etiologic origin, as it dictates a different management strategy. **Conclusions:** The distinct origins of avascular osteonecrosis due to corticosteroid use, medication-related osteonecrosis, and osteoradionecrosis converge on a common pathophysiological pathway: compromised vascular function leading to bone necrosis. This shared feature underscores the critical role of vascular health in maintaining bone integrity and facilitating repair processes. This literature review renders it important that future research should focus on developing targeted diagnostics and prevention protocols to optimize patient care and reduce morbidity.

Keywords: avascular osteonecrosis; medication-related osteonecrosis of the jaw; osteoradionecrosis

1. Introduction

Osteonecrosis of the jaw is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks in the absence of radiation to the head and neck [1]. It has frequently been associated with invasive dental procedures in patients at risk [2], although its pre-cise cause remains unknown. Jaw osteonecrosis includes several subtypes, some of which we chose to investigate in this review. These include medication-related osteonecrosis of the jaw (MRONJ), osteoradionecrosis (ORN), which are highly researched [3–6] and the newly emerging avascular or corticosteroid-induced osteonecrosis.

MRONJ is primarily linked to the use of antiresorptive and antiangiogenic medications, in-cluding bisphosphonates and denosumab, which are often prescribed for conditions like osteopo-rosis and metastatic bone disease [7]. ORN results from radiation therapy, commonly given for head and neck cancers [8]. The condition is marked by the failure of bone healing after radiation exposure and is often worsened by trauma or infection. Avascular osteonecrosis due to cortico-steroid use is considered the death of bone tissue due to lack of blood supply caused by the corti-costeroid therapy. It has been predominantly reported to affect the hip joint [9], but can also af-fect other regions, including the knee, shoulder, ankle, and jaws at last, which will be our main focus. The main jawbone blood supply is derived from one or more nutrient arteries, which pene-trate to the medulla and connect to the smaller periosteal arterial supply to enable perfusion of cortical bone [10]. When this pathway is

 doi:10.20944/preprints202505.0680.v1

interrupted, the blood flow to the bone is reduced or completely lost and this finally leads to the development of avascular osteonecrosis. Avascular osteonecrosis of the jaw due to corticosteroid use has been recently reported in cases of COVID-19 and in patients treated for autoimmune conditions [11,12].

This literature review focuses on discovering the detailed distinctions and similarities of the three mentioned subtypes of jaw osteonecrosis, which appears to be a significant clinical chal-lenge. Understanding the different causes, mechanisms, and symptoms of each subtype is essen-tial for accurate diagnosis and effective management. Ongoing research and clinical advance-ments continue to refine treatment approaches, aiming to improve patient outcomes and overall quality of life.

2. Aetio-Pathogenesis

Many theories have been suggested regarding the pathogenesis of jaw osteonecrosis, but the specific pathogenic mechanisms of each type are multifactorial [13]. Although avascular osteonecrosis, MRONJ, and osteoradionecrosis all lead to impaired blood supply and compromised bone healing in the jaw, their underlying pathophysiological processes differ significantly. Understanding their distinct differences is crucial for developing effective diagnostic and treatment protocols.

2.1. Medication-Related Osteonecrosis

Medication-related osteonecrosis of the jaw (MRONJ) is a severe condition associated with the prolonged use of antiresorptive and antiangiogenic drugs, primarily bisphosphonates, denosumab, and certain chemotherapeutic agents [14]. The pathogenesis of MRONJ is complex and multifactorial, involving impaired bone remodeling, suppression of angiogenesis, immune dysfunction [15], direct cellular toxicity and microbial infection [16]. While the precise mechanisms remain under investigation, current evidence suggests that these factors collectively contribute to the failure of normal bone healing and subsequent necrosis.

A key factor in MRONJ development is the inhibition of bone turnover caused by bisphosphonates and denosumab [17]. Bisphosphonates, which bind strongly to hydroxyapatite in bone, inhibit osteoclast-mediated bone resorption by disrupting osteoclast differentiation, function, and survival. This leads to an overall decrease in bone remodeling, resulting in the accumulation of microdamage over time and a reduced ability to repair bone after trauma [18]. Denosumab, a monoclonal antibody that targets RANKL (receptor activator of nuclear factor kappa-B ligand), also suppresses osteoclast activity by preventing osteoclast maturation [19]. Unlike bisphosphonates, it has been proven that denosumab does not incorporate into bone but has instead a prolonged effect on bone remodeling due to its mechanism of action. Both drugs lead to an imbalance in bone homeostasis, predisposing patients to necrosis, particularly in areas with high bone turnover such as the jaw.

Another significant contributor to MRONJ pathogenesis is the suppression of angiogenesis [20]. Antiangiogenic agents, commonly used in cancer therapy, interfere with vascular endothelial growth factor (VEGF) signaling, reducing the formation of new blood vessels [21]. This leads to a hypoxic environment within the jawbone, further compromising tissue repair and increasing susceptibility to necrosis. Bisphosphonates have also been shown to have antiangiogenic effects by inhibiting endothelial cell proliferation and function, thereby exacerbating the problem of poor vascular supply to bone tissue.

Direct toxicity to soft and hard tissues is another proposed mechanism underlying MRONJ [22]. Bisphosphonates can accumulate in the oral mucosa and bone, leading to cytotoxic effects on keratinocytes and fibroblasts [23]. This disrupts normal wound healing and epithelial repair, making patients more vulnerable to mucosal breakdown and subsequent bone exposure. Denosumab, though not incorporated into bone like bisphosphonates, also interferes with osteoclast function, leading to similar disruptions in tissue homeostasis [24]. This is different from bisphosphonates, which disrupt osteoclast function through intracellular mechanisms [25].

Immune dysfunction plays a critical role in the pathogenesis of MRONJ [26]. Both bisphosphonates and denosumab have been implicated in altering immune cell function, reducing the ability of the immune system to respond to infections and minor injuries. Additionally, cancer patients receiving antiresorptive or antiangiogenic therapy often experience further immunosuppression due to their underlying disease or concurrent chemotherapy, increasing their risk of secondary infections and impaired wound healing.

 doi:10.20944/preprints202505.0680.v1

Microbial infection is frequently observed in MRONJ lesions and may act as both a triggering and exacerbating factor [27]. Once the oral mucosa breaks down, the exposed necrotic bone becomes colonized by oral bacteria, leading to a chronic inflammatory state that further impairs healing. Actinomyces species are commonly identified in MRONJ lesions, suggesting a potential role in the disease progression [28]. However, whether infection is a primary cause or a secondary consequence of MRONJ remains a subject of ongoing research.

Trauma or mechanical stress, particularly from dental procedures such as extractions, is a well-documented risk factor for MRONJ [29]. Since the jawbone undergoes constant mechanical stress from mastication, even minor trauma can lead to mucosal breakdown and exposure of necrotic bone. In patients with suppressed bone remodeling and angiogenesis, these small injuries fail to heal properly, setting the stage for progressive bone necrosis.

Overall, MRONJ is the result of a convergence of multiple pathological processes, including inhibited bone turnover, vascular impairment, direct cellular toxicity, immune dysfunction, and microbial colonization.

2.2. Osteoradionecrosis of the Jaw

Unlike the other two types, osteoradionecrosis (ORN) of the jaw is a direct consequence of radiation therapy, commonly administered for head and neck cancers [30]. Radiation exposure damages not only the tumor but also the surrounding healthy tissues, including bone, by causing progressive tissue hypoxia, hypo-vascularity, and hypocellularity. The radiation-induced injury leads to fibrosis of blood vessels, reducing their ability to supply oxygen and nutrients to bone and soft tissue. As a result, bone cells (osteocytes, osteoblasts, and osteoclasts) suffer from impaired function, making the bone more susceptible to necrosis.

Furthermore, radiation also generates reactive oxygen species (ROS) and inflammatory cytokines, which contribute to chronic tissue inflammation and oxidative stress, further exacerbating bone damage. Even minor trauma, such as dental surgery or periodontal infections, can initiate a cascade of progressive necrosis in irradiated bone, leading to persistent non-healing wounds [31].

The mandible is particularly vulnerable to ORN, likely due to its greater cortical bone density and more critical vascularization, making it more susceptible to ischemic damage [32]. Additionally, the mandible is often included in the radiation field due to the location of primary tumors. The likelihood of developing ORN increases with radiation doses above 40–50 Gy, as higher doses lead to more extensive vascular damage and bone necrosis [33]. Beyond direct radiation effects, ORN risk is heightened by several contributing factors, including insufficient oral hygiene, pressure denture sores, and tumor localization in high-risk areas such as the tongue, alveolar process of the mandible, floor of the mouth, and retromolar region.

2.3. Avascular Osteonecrosis

Avascular osteonecrosis is a condition that arises primarily due to disrupted blood flow to the bone, leading to ischemia, necrosis, and subsequent bone deterioration. This form of osteonecrosis is often linked to prolonged or high-dose corticosteroid use.

The precise mechanisms involved in this condition include altered bone metabolism, increased intraosseous pressure within the jawbone, lipid metabolism dysfunction, defects in apoptosis and coagulation pathways, immune suppression, and the presence of underlying systemic comorbidities, such as diabetes or autoimmune diseases [34]. Corticosteroids can directly affect bone homeostasis by suppressing osteoblast activity, increasing osteoclast-mediated bone resorption, and reducing angiogenesis, thereby compromising the bone's ability to repair itself. Additionally, corticosteroids may promote fat embolism within the microvasculature of the bone, further exacerbating ischemia and leading to necrotic bone tissue over time [35–37]. Corticosteroids may directly affect bone cells, leading to apoptosis (programmed cell death) of osteocytes and other bone cells, which contributes to the necrotic process [38].

Conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are often treated with corticosteroids and are associated with a higher incidence of osteonecrosis [39].

The risk of osteonecrosis increases with high doses and prolonged use of corticosteroids. Intravenous pulses of methylprednisolone and high daily doses are particularly associated with higher risk. [40,41].

 doi:10.20944/preprints202505.0680.v1

How is Osteonecrosis of the Jaw Related to COVID-19 Infection?

Osteonecrosis of the jaw has been increasingly observed as a complication in patients who have had COVID-19. This condition involves the death of bone tissue due to disrupted blood supply, which can be exacerbated by factors associated with COVID-19.

COVID-19 is known to cause endothelial damage and abnormal blood clotting, which can lead to avascular necrosis (AVN) or osteonecrosis [42]. This vascular damage impairs blood flow to the bone, leading to tissue death.

The immune dysfunction and microvascular changes induced by COVID-19 may contribute to the development of osteomyelitis and osteonecrosis in the jaw [43]. These changes can lead to necrosis of the skeletal bones, including the jaw.

Many COVID-19 patients receive corticosteroid therapy, which is a known risk factor for osteonecrosis. Corticosteroids can impair bone healing and increase the risk of infections. In a study, all patients with post-COVID-19 osteonecrosis received corticosteroids [44].

COVID-19 patients are at higher risk for secondary infections, including fungal infections like mucormycosis and aspergillosis, which can lead to osteomyelitis and osteonecrosis of the jaw [45].

These infections are particularly aggressive and can cause significant bone destruction. Comorbid conditions such as diabetes mellitus, which is prevalent among COVID-19 patients, further increase the risk of developing osteonecrosis [46]. Diabetes can impair immune response and wound healing, making patients more susceptible to infections and bone necrosis.

2.4. Comparative Analysis and Common Pathophysiology (Author's Comment)

Despite their distinct origins—vascular ischemia in avascular osteonecrosis, suppressed bone remodeling in bisphosphonate-related osteonecrosis, and radiation-induced tissue injury in osteoradionecrosis—all three conditions ultimately share a fundamental feature: compromised vascular function leading to bone necrosis.

The inability of the bone to receive adequate blood supply prevents the necessary cellular and molecular processes required for repair and regeneration. While corticosteroids contribute to osteonecrosis by disrupting bone metabolism and increasing intraosseous pressure, bisphosphonates prevent normal bone turnover, and radiation therapy causes direct vascular and cellular damage. These different mechanisms underscore the complexity of osteonecrosis and highlight the need for tailored preventive and therapeutic strategies.

In clinical practice, understanding the distinctions among these forms of jaw osteonecrosis is essential for risk assessment, early diagnosis, and appropriate management. Patients receiving corticosteroids, bisphosphonates, or radiation therapy should be closely monitored for early signs of jawbone necrosis, and preventive measures such as maintaining good oral hygiene, avoiding invasive dental procedures when possible, and using adjunctive therapies like hyperbaric oxygen therapy in select cases should be considered.

3. Clinical Features

3.1. Clinical Presentation of Jaw Osteonecrosis

Osteonecrosis of the jaw (ONJ) lesions occur more frequently in the mandible (68%) than in the maxilla (28%) and are more prevalent in regions where the epithelium is thin and overlying bone prominences [47,48].

By the time clinical symptoms emerge, the disease is usually well-established, and patients often present with persistent, severe pain in the affected jaw area, which is considered a hallmark of the condition. This pain is typically localized, exacerbated by chewing, and may radiate to adjacent regions. One of the most distinguishing features of ONJ is the presence of exposed, necrotic bone with irregular edges, which can either be visible through the oral mucosa or palpable during clinical examinations. The necrotic bone is often surrounded by inflamed or ulcerated soft tissue, sometimes accompanied by purulent discharge, indicating secondary bacterial infection. As the disease progresses, the affected dentoalveolar segment may become mobile due to extensive bone destruction and loss of structural integrity.

Soft tissue swelling is a common finding and may be associated with intraoral or extraoral fistula formation, allowing drainage of infectious material [49]. In cases where the necrosis extends to the

 doi:10.20944/preprints202505.0680.v1

alveolar bone, adjacent teeth may become loose due to the weakening of the supporting periodontium.

Some patients also report altered sensations, including numbness or tingling in the affected jaw region [50], particularly when nerve compression or damage occurs. This sensory alteration is more commonly observed in the mandible due to the involvement of the inferior alveolar nerve. Additionally, oral malodor may develop as a result of bacterial overgrowth in necrotic tissue.

Delayed or non-healing wounds are another significant clinical feature, particularly at sites of previous dental extractions or surgical procedures [51], as the impaired blood supply prevents normal tissue regeneration. In more advanced cases, the progressive necrosis and structural weakening of the bone may lead to spontaneous or trauma-induced pathological fractures [52].

When secondary infections occur, systemic symptoms such as fever, malaise, and lymphadenopathy may be present, indicating the spread of infection beyond the localized jaw region. At the same time, radiological findings in advanced cases often reveal alterations in bone structure, with necrosis potentially extending into adjacent anatomical areas, such as the palatal raphe or maxillary sinus, further complicating the condition [53].

3.2. Clinical Presentation of Osteoradionecrosis (ORN)

Osteoradionecrosis, a severe complication of radiotherapy for head and neck malignancies, presents as a chronic non-healing wound in the previously irradiated area of the jaw. The condition typically begins with mucosal inflammation and ulceration, followed by progressive exposure of necrotic bone that persists for at least three months [54]. Patients often report localized pain, which may initially be mild but often progresses to severe, deep, and radiating pain that is refractory to standard analgesic treatment [55].

This pain may be exacerbated by secondary infection, which is common in ORN due to the exposed necrotic bone serving as a reservoir for bacterial colonization [56]. The affected area often exhibits swelling, erythema, and purulent discharge, with some cases developing foul-smelling intraoral or extraoral sinus tracts [57].

The necrotic bone, frequently located in the mandible due to its limited vascular supply and higher radiation absorption, may exhibit purulent discharge, sometimes associated with intraoral or extraoral sinus tracts. As bone necrosis advances, the affected bone may become fragile and brittle, predisposing patients to pathological fractures, particularly in the mandible, which bears the highest mechanical stress [58], significantly impairing oral function and quality of life.

Fibrosis and soft tissue contracture in the irradiated region can lead to restricted mandibular movements (trismus), significantly impairing mastication, speech, and oral hygiene maintenance [59].

Radiographic findings often correlate with clinical severity. While early ORN may appear as ill-defined areas of radiolucency, advanced cases show moth-eaten bone destruction, sequestration, and cortical thinning, sometimes extending beyond the initially irradiated field [60]. The chronic and progressive nature of ORN underscores the importance of early recognition and intervention to mitigate severe complications and improve patient outcomes.

3.3. Clinical Presentation of Avascular Osteonecrosis of the Jaw

Avascular osteonecrosis of the jaw is not traditionally recognized as a well-documented complication of corticosteroid use, but there is emerging evidence which suggests an increasing number of cases, particularly in the wake of the COVID-19 pandemic [61–63].

It is accepted that corticosteroids have been widely utilized for their potent anti-inflammatory and immunosuppressive properties, playing a crucial role in managing conditions such as autoimmune diseases, organ transplantation, and, more recently, severe COVID-19 cases. However, their prolonged or high-dose administration has been linked to systemic osteonecrosis, with growing reports implicating them in jawbone necrosis. Additionally, the use of corticosteroids in treating conditions like asthma, eczema, and other inflammatory diseases is also linked to the development of osteonecrosis due to their impact on bone remodeling and blood supply [64].

The clinical presentation of corticosteroid-induced ONJ closely resembles other forms of jaw osteonecrosis, but is often insidious in onset, with symptoms developing from weeks to months after corticosteroid exposure. All of the published case reports that were examined about avascular

 doi:10.20944/preprints202505.0680.v1

osteonecrosis related to corticosteroid use had 2 common features: history of long-term usage of steroids and a recent tooth extraction or dental surgical intervention.

According to the results from post-COVID oral manifestations in patients with osteonecrosis in the examined studies:

1. All reported patients with post-COVID osteonecrosis had received corticosteroid prescriptions. Corticosteroids are commonly used for their anti-inflammatory and immunosuppressive properties, but their prolonged use can lead to significant adverse effects, including osteonecrosis [65].
2. Almost all patients exhibited osteonecrosis of the maxillary bone. This condition often occurred spontaneously and unprovoked, with the onset of jaw necrosis typically appearing 3-12 weeks post-COVID. The literature indicates that COVID-19 can predispose individuals to osteonecrosis due to thrombotic inflammatory phenomena and the therapeutic use of corticosteroids [66].
3. The symptoms observed in these patients included a mobile dentoalveolar maxillary segment, which indicates a severe impact on the structural integrity of the jawbone, and a pus-oozing fistula, a common sign of infection and necrosis in the affected bone. Additionally, palatal swelling was noted, often associated with underlying inflammatory or infectious processes. A hallmark of osteonecrosis was also observed in the form of exposed necrotic bone with oral mucosal ulceration, where the necrotic bone becomes visible due to the ulceration of the overlying mucosa.

Except for the specific clinical manifestation of osteonecrosis in the COVID cases, the disease also presents with the usual symptoms of any other type of jaw osteonecrosis. These include—persistent pain in the affected jaw, presence of exposed, necrotic bone, surrounded by inflamed or ulcerated soft tissue and delayed or non-healing wounds. Radiological examination often reveals characteristic changes in bone architecture, with areas of sclerosis and sequestration.

It's evident that corticosteroid-induced ONJ necessitates timely intervention, including surgical debridement, antibiotic therapy, and careful long-term monitoring to prevent disease progression and complications.

3.4. Comparative Analysis of Medication-Related, Osteoradionecrosis and Avascular Osteonecrosis Due to Corticosteroid Use (Author's Comment)

While avascular osteonecrosis due to corticosteroid use, MRONJ, and osteoradionecrosis share the common endpoint of impaired bone healing due to vascular compromise, their pathophysiology, clinical presentation, and progression may vary significantly.

Avascular (corticosteroid-related) ONJ arises due to corticosteroids' effects on bone metabolism, microvascular circulation, and immune function. It typically manifests in patients with prolonged corticosteroid use, often following a spontaneous onset with/without prior trauma or dental procedures. The condition is characterized by exposed necrotic bone, pain, soft tissue inflammation, and delayed wound healing. Unlike MRONJ and ORN, this type of ONJ is more commonly associated with systemic conditions requiring immunosuppressive therapy rather than a direct pharmacologic effect on bone turnover.

MRONJ, on the other hand, occurs predominantly in patients receiving antiresorptive medications such as bisphosphonates or denosumab, particularly for osteoporosis or malignancies.

The primary mechanism involves the suppression of bone turnover and angiogenesis, leading to an inability to repair microdamage and maintain healthy bone.

Osteoradionecrosis differentiates itself from the other two by developing as a consequence of radiation therapy to the head and neck region, resulting in chronic hypoxia, hypo-cellularity, and hypo-vascularity in the affected bone. This condition is distinct from both corticosteroid-induced ONJ and BRONJ in that its primary etiology is radiation-induced tissue fibrosis and endothelial damage rather than pharmacologic effects.

4. Material and Methods

This review synthesized data from scientific studies and articles on jaw osteonecrosis and corticosteroid use. A PubMed and Scopus database search was used to identify case reports, reviews and articles that were published, using keywords such as "osteonecrosis", "jaw", "mandible" and

 doi:10.20944/preprints202505.0680.v1

"corticosteroid therapy". Sources were selected based on relevance and reliability, providing a comprehensive overview of the associations between corticosteroid use and avascular osteonecrosis of the jaws. Specific focus was placed on publications detailing its pathophysiology, clinical presentation, and treatment outcomes in such cases.

5. Results

Overall findings indicated that patients with avascular osteonecrosis (AON) due to corticosteroid use, medication-related osteonecrosis of the jaw (MRONJ), or osteoradionecrosis (ORN) all share a common endpoint of impaired bone healing due to vascular compromise, leading to bone necrosis. Despite the different mechanisms at play, the shared outcome of vascular dysfunction in all three conditions highlights the need for individualized approaches in diagnosis and treatment.

6. Conclusions

While all three forms of the discussed jaw osteonecrosis share overlapping clinical features, their underlying aetio-pathogeneses dictate differences in risk factors and pathways of progression. Corticosteroid-induced ONJ often occurs in immunocompromised patients after the long-term use of corticosteroids, MRONJ is strongly associated with antiresorptive or anti-angiogenic therapy and dental trauma, and ORN is a delayed complication of radiotherapy-induced vascular damage. Understanding these distinctions is crucial for early diagnosis, risk assessment, and highlighting the need for research about tailored treatment approaches to optimize patient outcomes.

Acknowledgments: The author would like to express her sincere gratitude to Dr. Konstantin Stamatov for his invaluable advice and insights on the subject and to Dr. Bozhidar Soytariev for his support and encouragement to pursue and complete this work.

References

1 Ruggiero et al., "American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update."
2 Wong, Tay, and Chieng, "Osteonecrosis of Mandible."
3 Bassan Marinho Maciel et al., "Etiopathogenesis of Medication-Related Osteonecrosis of the Jaws."
4 Santos-Silva, *Clinical Decision-Making in Oral Medicine*.
5 Chronopoulos et al., "Osteoradionecrosis of the Jaws."
6 Coulthard and Dave, "Osteoradionecrosis of the Jaws and Management Strategies."
7 Thomas and Ouanounou, "Medication-Related Osteonecrosis of the Jaw."
8 Chronopoulos et al., "Osteoradionecrosis of the Jaws."
9 "Avascular Necrosis (Osteonecrosis)-Avascular Necrosis (Osteonecrosis)—Symptoms & Causes."
10 Marenzana and Arnett, "The Key Role of the Blood Supply to Bone."
11 Al-Mahalawy et al., "Post-COVID-19 Related Osteonecrosis of the Jaw (PC-RONJ)."
12 Ghaleb, Omar, and Ibrahim, "Avascular Necrosis of Bone in Systemic Lupus Erythematosus."
13 Bassan Marinho Maciel et al., "Etiopathogenesis of Medication-Related Osteonecrosis of the Jaws."
14 Jiang et al., "Medication-Related Osteonecrosis of the Jaw (MRONJ)."
15 Frutuoso et al., "Medication-Related Osteonecrosis of the Jaw."
16 Shamsoddin et al., "Etiologic Role of Bacterial Microorganisms in Medication Related Osteonecrosis of the Jaws: A Systematic Review."
17 Bassan Marinho Maciel et al., "Etiopathogenesis of Medication-Related Osteonecrosis of the Jaws."
18 Srivichit et al., "Impacts of Bisphosphonates on the Bone and Its Surrounding Tissues."
19 Farias et al., "Three-Year Effect of Bisphosphonates on Bone Mineral Density after Denosumab Withdrawal."
20 Ruggiero et al., "Medication-Related Osteonecrosis of the Jaw—2022 Update."
21 Lopes-Coelho et al., "Anti-Angiogenic Therapy."
22 Bullock et al., "A Review Into the Effects of Pamidronic Acid and Zoledronic Acid on the Oral Mucosa in Medication-Related Osteonecrosis of the Jaw."
23 Basso et al., "Cytotoxic Effects of Zoledronic Acid on Human Epithelial Cells and Gingival Fibroblasts."

 doi:10.20944/preprints202505.0680.v1

24 Ferrari and Langdahl, "Mechanisms Underlying the Long-Term and Withdrawal Effects of Denosumab Therapy on Bone."
25 Baron, Ferrari, and Russell, "Denosumab and Bisphosphonates."
26 Zhang et al., "The Role of the Immune Response in the Development of Medication-Related Osteonecrosis of the Jaw."
27 Kim et al., "Can Medication-Related Osteonecrosis of the Jaw Be Attributed to Specific Microorganisms through Oral Microbiota Analyses?"
28 Kövér et al., "Role of Actinomyces Spp. and Related Organisms in the Development of Medication-Related Osteonecrosis of the Jaw (MRONJ)."
29 Lara et al., "A Systematic Review Assessing Occurrence of Medication-Related Osteonecrosis of the Jaw Following Dental Procedures."
30 Singh et al., "Osteoradionecrosis of the Jaw."
31 Kim, Jenrow, and Brown, "Mechanisms of Radiation-Induced Normal Tissue Toxicity and Implications for Future Clinical Trials."
32 Gaêta- Araujo et al., "Osteomyelitis, Osteoradionecrosis, or Medication- related Osteonecrosis of the Jaws?"
33 Saunders et al., "Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy."
34 Motta et al., "Steroid-Induced Osteonecrosis."
35 Skácelová et al., "Osteonekróza Asociovaná Se Systémovou Kortikoterapií."
36 Lafforgue, "Pathophysiology and Natural History of Avascular Necrosis of Bone."
37 Chang, Greenspan, and Gershwin, "The Pathogenesis, Diagnosis and Clinical Manifestations of Steroid-Induced Osteonecrosis."
38 Chang, Greenspan, and Gershwin.
39 Ghaleb, Omar, and Ibrahim, "Avascular Necrosis of Bone in Systemic Lupus Erythematosus."
40 Skácelová et al., "Osteonekróza Asociovaná Se Systémovou Kortikoterapií."
41 Ce et al., "Avascular Necrosis of the Bones."
42 Dar-Odeh et al.
43 V.I. Razumovsky Saratov State Medical University. Saratov, Russia et al., "POSTCOVID NECROSIS OF THE MAXILLOFACIAL REGION."
44 Al-Mahalawy et al., "Post-COVID-19 Related Osteonecrosis of the Jaw (PC-RONJ)."
45 Datarkar et al., "Osteomyelitis of Jaw Bone Due to Aspergillosis in Post-COVID-19 Patients."
46 Vardas et al., "Impact of COVID-19 Disease on the Development of Osteomyelitis of Jaws."
47 Lo Giudice et al., "Is the Mandibular Condyle Involved in Medication-Related Osteonecrosis of the Jaw?"
48 Wasserzug et al., "Involvement of the Maxillary Sinus in Bisphosphonate-Related Osteonecrosis of the Jaw."
49 Sedghizadeh and Jones, "Osteonecrosis of the Jaw."
50 Sedghizadeh and Jones.
51 Borromeo et al., "A Large Case-Control Study Reveals a Positive Association Between Bisphosphonate Use and Delayed Dental Healing and Osteonecrosis of the Jaw."
52 Otto et al., "Pathologic Fractures in Bisphosphonate-Related Osteonecrosis of the Jaw—Review of the Literature and Review of Our Own Cases."
53 Otto et al.
54 Chronopoulos et al., "Osteoradionecrosis of the Jaws."
55 Peterson et al., "Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy."
56 Ajila and Hegde, "Osteoradionecrosis—a Review of Clinical Features and Management."
57 Singh et al., "Osteoradionecrosis of the Jaw."
58 Ohori et al., "Risk Factors for Pathological Fracture in Patients with Mandibular Osteoradionecrosis."
59 Brook, "Late Side Effects of Radiation Treatment for Head and Neck Cancer."
60 Walter and Renné, "Osteomyelitis, Osteoradionecrosis, and Medication-Related Osteonecrosis of Jaws."
61 Mañón et al., "COVID-Associated Avascular Necrosis of the Maxilla—A Rare, New Side Effect of COVID-19."

 doi:10.20944/preprints202505.0680.v1

62 Boymuradov et al., “Complications of COVID-19 in the Maxillo-Facial Region.”
63 Grillo et al., “Two Cases of COVID-Related Osteonecrosis of the Jaws: A New and Worrying Entity Is Emerging.”
64 Rupprecht and Krishnaswamy, “Osteonecrosis.”
65 Koshi et al., “Complications of Corticosteroid Therapy.”
66 Dar-Odeh et al., “Jaw-Related Complications in COVID-19 Patients; a Systematic Review.”