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Medication-Related Post-COVID-19 Osteonecrosis of the Jaw: An Interprofessional Approach to Prevention, Diagnosis, and Management.

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Abstract

Background: Post-COVID-19 osteonecrosis of the jaw (PC-ONJ) has emerged as an uncommon but clinically significant complication reported after SARS-CoV-2 infection. Its development may involve multiple interacting factors, including corticosteroid exposure, diabetes mellitus, immunosuppression, vascular injury, and secondary infections. COVID-associated mucormycosis (CAM) represents a particularly aggressive form that can cause extensive maxillofacial destruction and life-threatening complications.

Aim: This review examines the clinical presentation, risk factors, diagnostic challenges, and current management strategies for PC-ONJ, with particular attention to differentiating non-fungal osteonecrotic lesions from CAM.

Methods: A narrative review of the relevant literature was conducted to summarize reported clinical manifestations, proposed pathogenic mechanisms, diagnostic approaches, treatment options, and outcomes. Evidence concerning medical and surgical interventions, adjunctive therapies, and preventive measures was also considered.

Results: PC-ONJ presents with variable manifestations, including persistent facial pain, swelling, tooth mobility, exposed bone, fistulas, and delayed wound healing. The maxilla is frequently affected, and lesions may extend into the paranasal sinuses and adjacent structures. Diagnosis remains challenging because clinical and radiological findings overlap with osteomyelitis, medication-related osteonecrosis, osteoradionecrosis, malignancy, and invasive fungal infections. Management depends on the underlying pathology and disease extent. CAM requires prompt systemic antifungal therapy and surgical debridement, whereas non-fungal lesions may respond to conservative measures, antibiotics when indicated, and appropriate surgery.

Conclusion: Early recognition, accurate etiological assessment, metabolic control, and multidisciplinary management are essential to improve outcomes and reduce complications.

Keywords: COVID-19; osteonecrosis of the jaw; mucormycosis; maxillofacial complications; corticosteroids; diabetes mellitus; diagnosis; management.

Introduction

Since its emergence in late 2019, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved from being primarily recognized as a respiratory illness to a complex systemic disease with multisystem manifestations. Although the respiratory system represents the principal site of acute infection, accumulating evidence indicates that coronavirus disease 2019 (COVID-19) can affect multiple organs through direct viral injury, endothelial dysfunction, dysregulated immune responses, systemic inflammation, and disturbances in coagulation pathways. These pathological changes may persist

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beyond the acute phase of infection, contributing to a heterogeneous spectrum of post-acute complications collectively described as post-COVID-19 conditions or post-acute sequelae of SARS-CoV-2 infection (PASC) [1,2]. As the population of COVID-19 survivors continues to grow, increasing attention has been directed toward identifying delayed complications involving the cardiovascular, neurological, renal, musculoskeletal, endocrine, and oral and maxillofacial systems [3,4]. Among the less frequently recognized complications, osteonecrotic and osteomyelitic lesions of the maxilla and mandible have emerged as clinically important manifestations reported following SARS-CoV-2 infection. Since 2020, clinical reports have documented cases of jawbone necrosis developing weeks or months after recovery from COVID-19. Initial observations were frequently associated with COVID-19-associated mucormycosis (CAM), particularly in patients with diabetes mellitus, severe immunosuppression, or prolonged corticosteroid exposure. However, subsequent reports have also described similar lesions in patients without confirmed invasive fungal infection or established conventional risk factors for medication-related or radiation-related osteonecrosis [5,6]. This evolving clinical presentation has generated several descriptive terms, including COVID-19-related osteonecrosis of the jaw (CRONJ), post-COVID-19 osteonecrosis of the jaw (PC-ONJ), post-COVID-19-related osteonecrosis (PC-RONJ), and post-COVID-19 osteomyelitis. The absence of universally accepted diagnostic terminology and classification criteria reflects the complexity and potentially heterogeneous nature of these conditions.

The clinical presentation of post-COVID-19 jawbone lesions varies considerably according to the underlying pathological process, anatomical location, extent of tissue involvement, and presence of secondary infection. Common manifestations include persistent facial or jaw pain, dental mobility, nonhealing extraction sockets, exposed necrotic bone, gingival or palatal ulceration, purulent discharge, intraoral or extraoral fistulae, and maxillary sinus involvement. In some patients, pain, swelling, tooth sensitivity, and unexplained dental mobility may precede clinically detectable bone exposure by several weeks or months. This interval between initial symptoms and the appearance of characteristic lesions can delay diagnosis and complicate differentiation from conventional odontogenic infections, chronic suppurative osteomyelitis, medication-related osteonecrosis of the jaw (MRONJ), and osteoradionecrosis (ORN) [5,7]. Furthermore, radiological investigations may demonstrate osteolytic changes, cortical destruction, sequestration, periosteal reactions, and disruption of normal trabecular architecture. Nevertheless, these findings are not specific to post-COVID-19 osteonecrosis and must be interpreted alongside clinical findings, medical history, microbiological investigations, and histopathological assessment [8]. The pathogenesis of post-COVID-19 jawbone complications remains incompletely understood and is increasingly considered multifactorial. One proposed mechanism involves COVID-19-associated endothelial injury and hypercoagulability, which may promote microvascular thrombosis and compromise blood supply to the maxillary and mandibular bones. Because normal bone remodeling and tissue repair depend on adequate vascular perfusion, persistent microcirculatory disturbances may contribute to localized ischemia, impaired osteocyte viability, and progressive bone necrosis. In parallel, SARS-CoV-2-associated inflammatory responses, cytokine dysregulation, and alterations in angiotensin-converting enzyme 2 (ACE2)-related pathways may further affect vascular integrity and tissue homeostasis [1,7,9]. Additional contributing factors include immune dysfunction, pre-existing diabetes mellitus, uncontrolled hyperglycemia, malnutrition, prolonged hospitalization, and treatment-related complications, particularly systemic corticosteroid exposure. These factors may independently or collectively impair wound healing, reduce host defense mechanisms, and increase susceptibility to secondary bacterial or fungal infections.

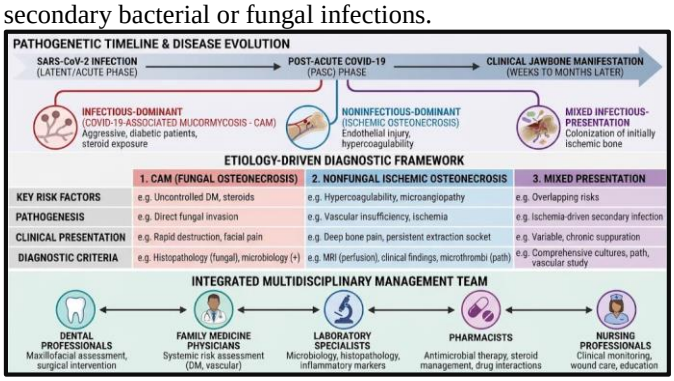


Figure-1: Overview of post-COVID-19 Osteonecrosis of the Jaw.

An important consideration is the distinction between infectious and noninfectious forms of post-COVID-19 jawbone disease. In some patients, invasive fungal infection, particularly mucormycosis, represents the principal pathological mechanism responsible for aggressive tissue destruction and progressive osteonecrosis. Such cases require prompt microbiological and histopathological confirmation and appropriate antifungal treatment. Conversely, other patients demonstrate clinical and radiological evidence of bone necrosis without convincing evidence of invasive fungal infection, suggesting that vascular compromise, post-inflammatory tissue injury, or other noninfectious mechanisms may predominate [7,10]. A third group may exhibit overlapping ischemic and infectious processes, in which initially compromised bone subsequently becomes colonized or infected by bacterial or fungal

organisms. Recognizing these potential phenotypes is essential because their diagnostic pathways, therapeutic requirements, and prognostic implications may differ substantially. Despite the growing number of published reports, several important limitations continue to affect the understanding and management of these complications. The available literature predominantly consists of individual case reports and small observational case series, with limited prospective evidence and insufficient long-term follow-up. Diagnostic definitions remain inconsistent, and the terms osteonecrosis and osteomyelitis are sometimes used interchangeably despite representing distinct pathological processes. Moreover, investigations do not consistently include comprehensive fungal and bacterial cultures, tissue histopathology, vascular assessment, or systematic evaluation of predisposing systemic conditions. These limitations may result in diagnostic misclassification, unnecessary antifungal treatment, delayed surgical intervention, or failure to recognize underlying ischemic bone injury [5,11].

Accordingly, a comprehensive understanding of post-COVID-19 jawbone complications requires an integrated clinical approach involving dental professionals, family medicine physicians, laboratory specialists, pharmacists, and nursing professionals. Dentists play a central role in identifying oral manifestations, assessing dental and maxillofacial involvement, and determining the need for surgical intervention. Family medicine physicians contribute to the assessment and management of systemic risk factors, including diabetes mellitus, vascular disorders, and immunosuppression. Laboratory specialists support diagnostic differentiation through inflammatory markers, glycemic assessment, microbiological cultures, and histopathological investigations. Pharmacists contribute to the evaluation of corticosteroid exposure, antimicrobial selection, antifungal therapy, drug interactions, and medication safety. Nursing professionals support clinical monitoring, wound care, pain assessment, medication administration, and patient education. Such collaboration is particularly important in patients with complex presentations and multiple comorbidities. This review aims to provide a comprehensive and critical synthesis of the available evidence concerning post-COVID-19 osteonecrosis and osteomyelitis of the jaws. Its central contribution is an etiology-driven framework that distinguishes among COVID-19-associated mucormycosis, nonfungal ischemic osteonecrosis, and mixed infectious-ischemic presentations rather than treating all reported cases as a single pathological entity. The review examines epidemiological characteristics, proposed pathogenic mechanisms, clinical manifestations, radiological and histopathological findings, diagnostic criteria, differential diagnoses, and current therapeutic strategies. Particular attention is directed toward distinguishing true post-viral bone injury from established causes of jaw osteonecrosis and identifying the clinical circumstances that support an infectious or noninfectious diagnosis. By integrating evidence from dental, medical, laboratory, pharmacological, and nursing perspectives, this review seeks to clarify existing diagnostic uncertainties, support evidence-based clinical decision-making, and identify priorities for future research, including the development of standardized case definitions, diagnostic algorithms, and multidisciplinary management protocols.

Evolution of Terminology

Jaw osteonecrosis (ONJ) refers to bone tissue death affecting the maxilla or mandible due to disruption of normal bone homeostasis. Historically, several terms have been used to describe this condition, reflecting different assumptions regarding its underlying mechanisms. Early terminology included "aseptic necrosis," which distinguished noninfectious bone destruction from septic osteomyelitis. Subsequently, the terms "avascular necrosis" and "ischemic necrosis" emphasized impaired blood supply as the principal cause of bone death. However, contemporary evidence indicates that jaw osteonecrosis involves multiple interacting mechanisms, including vascular impairment, altered bone remodeling, cellular toxicity, inflammation, impaired angiogenesis, systemic disease, and secondary infection [12–14]. During the 1990s, the Association Research Circulation Osseous (ARCO) adopted "osteonecrosis" as the preferred terminology, although expressions such as avascular necrosis remain common in clinical literature [15]. Current understanding supports using osteonecrosis as the general descriptive term because not all cases result primarily from vascular insufficiency. The use of more specific etiological modifiers is therefore recommended to avoid diagnostic oversimplification and guide appropriate management [12,13].

Current Consensus Terminology for the Jaws

Osteonecrosis of the jaw represents an umbrella classification encompassing several etiological categories, including medication-related, radiation-related, traumatic, nontraumatic systemic or infectious, and spontaneous or idiopathic forms [13]. Medication-related osteonecrosis of the jaw (MRONJ) is the accepted terminology for medication-associated bone necrosis. It replaced earlier terms such as bisphosphonate-related osteonecrosis of the jaw (BRONJ) to include a broader range of causative medications. These include bisphosphonates, denosumab, antiangiogenic agents, and targeted therapies such as bevacizumab and sunitinib. The conventional diagnostic criteria include current or previous exposure to these medications, exposed bone or bone detectable through an intraoral or extraoral fistula persisting for more than eight weeks, and no history of jaw irradiation or metastatic disease involving the

jawbones [14,16]. Osteoradionecrosis (ORN) describes necrosis of previously irradiated jawbone, particularly following radiotherapy for head and neck malignancies. It is traditionally characterized by exposed irradiated bone that fails to heal for at least three months without evidence of persistent or recurrent malignancy. Its pathogenesis involves radiation-induced hypoxia, reduced vascularity, decreased cellularity, and fibrosis, resulting in impaired bone remodeling and wound healing [13]. Traumatic ONJ develops following mechanical, thermal, or chemical injury. Causes include maxillofacial fractures, surgical procedures, aggressive curettage, prolonged tissue pressure, and exposure to chemical agents such as sodium hypochlorite or strong acids. In contrast, nontraumatic ONJ develops without direct injury and may accompany systemic or infectious conditions. Associated infections include bacterial osteomyelitis, actinomycosis, tuberculosis, syphilis, mucormycosis, and aspergillosis. Systemic predisposing conditions include diabetes mellitus, coagulation abnormalities, hemoglobinopathies, autoimmune disorders, immunodeficiency, and vascular diseases. Malignancies and exposure to certain illicit substances, including cocaine and desomorphine, may also contribute to jawbone necrosis [13,17]. Spontaneous or idiopathic ONJ refers to exposed bone lesions without identifiable medication exposure, radiotherapy, trauma, or underlying systemic disease. Such lesions may occur over anatomical prominences, including mandibular and palatal tori or exostoses, and are sometimes described as oral ulceration with bone sequestration [13]. Historically, phosphorus-related jaw necrosis, known as "phossy jaw," occurred among match factory workers exposed to white phosphorus [18]. Overall, current terminology favors ONJ as the general classification, supplemented by specific etiological descriptions such as MRONJ, ORN, traumatic ONJ, infection-related ONJ, and idiopathic ONJ. This classification provides a clearer basis for distinguishing post-COVID-19 jawbone complications from established forms of osteonecrosis.

Etiologic Classification of Jaw Osteonecrosis

Jaw osteonecrosis (ONJ) can be classified according to its underlying etiology, reflecting the diverse mechanisms responsible for impaired bone viability and tissue destruction. This classification includes several major categories. Medication-related osteonecrosis of the jaw (MRONJ) is associated with antiresorptive agents, including bisphosphonates and denosumab, as well as antiangiogenic and targeted therapies such as bevacizumab, sunitinib, tyrosine kinase inhibitors, and mTOR inhibitors. Its pathogenesis involves suppressed bone remodeling, impaired angiogenesis, direct soft-tissue toxicity, and secondary infection [14,19,20]. Osteoradionecrosis (ORN) develops following therapeutic radiation involving the jaws, particularly at cumulative doses exceeding approximately 50–60 Gy. Radiation-induced vascular injury, endarteritis, tissue hypoxia, fibrosis, and reduced cellularity contribute to impaired bone remodeling and wound healing [21]. Traumatic ONJ results from mechanical, chemical, or thermal injuries, including maxillofacial fractures, osteotomies, surgical procedures, aggressive curettage, sodium hypochlorite accidents, excessive drilling heat, and exposure to devitalizing agents or strong acids [13]. Infection-related ONJ develops in association with bacterial, viral, or fungal infections. Associated conditions include chronic osteomyelitis, noma, tuberculosis, syphilis, actinomycosis, mucormycosis, aspergillosis, and herpes zoster-associated lesions. These conditions may produce extensive bone destruction and surrounding soft-tissue involvement [13]. Systemic disease-associated ONJ occurs in patients with conditions affecting vascular perfusion, immunity, or bone metabolism. Predisposing disorders include uncontrolled diabetes mellitus, coagulation abnormalities, hematological diseases, autoimmune disorders, and vascular conditions [13,14,18,22]. Neoplasm-associated ONJ results from primary or metastatic malignancies infiltrating and destroying jawbone tissue. Excluding malignant involvement is essential before establishing an MRONJ diagnosis [23,24]. Substance-associated osteonecrosis may follow exposure to substances such as cocaine and desomorphine, which cause vascular compromise and chemical tissue injury [17,25]. Finally, idiopathic or spontaneous ONJ describes exposed bone or small sequestra without an identifiable medication-related, traumatic, infectious, radiation-related, or systemic cause. These lesions frequently occur over anatomical prominences, particularly along the lingual mandibular surface [26]. This etiological classification complements clinical staging systems, which assess symptoms, exposed bone, and the anatomical extent of disease.

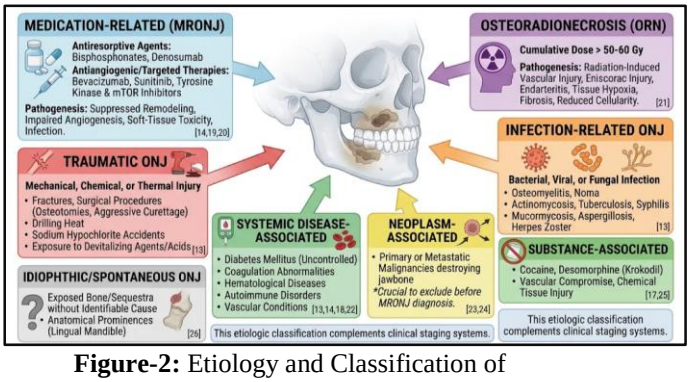


Figure-2: Etiology and Classification of osteonecrosis of Jaw.

Clinical Staging and Classification Systems

The American Association of Oral and Maxillofacial Surgeons (AAOMS) introduced its staging system in 2006, with subsequent revisions in

2009, 2014, and 2022. It remains the most widely used classification for medication-related osteonecrosis of the jaw (MRONJ) [16,24]. The system includes an at-risk category for patients with previous or current exposure to relevant medications without clinical evidence of bone necrosis. Stage 0 represents a non-exposed variant characterized by nonspecific symptoms or radiographic abnormalities, including jaw pain, tooth mobility, bone sclerosis, periodontal ligament widening, and delayed socket healing. Stage 1 involves exposed necrotic bone or a fistula probing to bone without pain or clinical signs of infection. Stage 2 is characterized by exposed or probeable necrotic bone accompanied by pain, erythema, and infection, sometimes with purulent discharge. Stage 3 represents advanced disease, involving necrotic bone with pain and infection, together with complications such as pathological fracture, extraoral fistula, oroantral or oronasal communication, or extensive osteolysis reaching the inferior mandibular border or maxillary sinus floor [16,18,24,27,28]. This classification supports treatment planning according to disease severity, ranging from conservative management to surgical intervention. Unlike MRONJ, osteoradionecrosis (ORN) lacks a universally accepted staging system. The Morton and Simpson classification (1986) categorizes ORN according to clinical progression, distinguishing limited bone exposure, sequestration, and extensive necrosis associated with fistulas or pathological fractures. The severity of disease determines whether conservative treatment or surgical intervention is required [13,29]. Another recognized system is the Kagan and Schwartz classification (2002), which considers bone involvement and soft-tissue destruction. Stage I involves superficial cortical disease with limited soft-tissue ulceration, whereas Stage II indicates medullary extension and is subdivided according to the extent of soft-tissue damage and fistula formation. Stage III represents extensive bone necrosis and may involve pathological fractures, fistulas, or overlying tissue necrosis. Further subdivisions distinguish limited from extensive soft-tissue involvement, with advanced cases frequently requiring surgical resection and reconstruction [13]. More recent consensus efforts have incorporated clinical manifestations, imaging findings, and radiation history into ORN assessment, although classification approaches remain variable across clinical guidelines [29].

Epidemiology and Risk Factors of Post-COVID-19 Osteonecrosis of the Jaw

Since mid-2020, more than 200 cases of post-COVID-19 jaw osteonecrosis and osteomyelitis have been reported worldwide. A systematic review encompassing 42 studies identified 201 cases, highlighting this complication as an uncommon but increasingly recognized post-infectious condition. The median patient age ranged between 50 and 55 years, although cases have occurred across different age groups. Males represented approximately three-quarters of reported patients, potentially reflecting their greater susceptibility to severe COVID-19 and associated metabolic and inflammatory disturbances. Diabetes mellitus was the most frequently reported comorbidity, affecting approximately 65% of patients and representing an important predisposing factor, particularly when poorly controlled [5,30]. Anatomically, the maxilla is considerably more frequently affected than the mandible, accounting for approximately 90% of reported cases, whereas mandibular involvement represents fewer than 10%. This distribution differs from conventional osteomyelitis, which more commonly affects the mandible. The predominance of maxillary involvement may partly reflect the association between post-COVID-19 jaw complications and invasive fungal infections, particularly mucormycosis, which frequently originates in the sinonasal region and extends into adjacent maxillary structures. Additionally, COVID-19-associated endothelial injury, microvascular thrombosis, and impaired tissue perfusion may contribute to maxillary bone susceptibility [5,31–33]. Other potential risk factors include corticosteroid exposure, immunosuppression, hyperglycemia, and severe systemic inflammation.

Key Risk Factors

Post-COVID-19 osteonecrosis of the jaw (PC-ONJ) is associated with multiple interacting risk factors, particularly corticosteroid therapy, diabetes mellitus, immunosuppression, severe COVID-19, and local dental trauma. Corticosteroid therapy represents an important predisposing factor, with approximately 58.5% of reported PC-ONJ patients having received corticosteroids during COVID-19 treatment [5]. Although corticosteroids reduce excessive inflammation, prolonged or high-dose exposure suppresses immunity, increases susceptibility to bacterial and fungal infections, and impairs bone healing. Furthermore, steroid-induced hyperglycemia may worsen pre-existing diabetes or precipitate new-onset glucose intolerance. These effects are particularly relevant to mucormycosis, for which corticosteroid exposure has been frequently documented [34–39]. Diabetes mellitus is another major risk factor, affecting approximately two-thirds of reported PC-ONJ patients. Poor glycemic control compromises neutrophil function, damages vascular endothelium, and delays tissue repair. Diabetic ketoacidosis further increases susceptibility to mucormycosis by creating favorable metabolic conditions for fungal proliferation. Consequently, appropriate glycemic control is essential for reducing infectious and ischemic complications [5,40–42]. Severe COVID-19 and hospitalization may contribute through systemic inflammation, endothelial injury, hypercoagulability, prolonged immobilization, and exposure to invasive procedures and broad-spectrum

antibiotics. Nevertheless, cases following mild or moderately symptomatic infections indicate that hospitalization is not a prerequisite [5]. Additional immunosuppressive conditions, including malignancy, transplantation, and immunomodulatory treatment such as tocilizumab, may further increase susceptibility to opportunistic infections and impair bone healing [31,33,41,43,44]. Local dental factors, particularly tooth extraction, periodontal disease, and poorly fitting dentures, may initiate mucosal injury and expose underlying bone. Demographically, reported cases predominantly involve middle-aged and older adults, with male predominance, although pediatric cases have also occurred [5,6,45]. Overall, current evidence does not establish SARS-CoV-2 infection as an independent cause of ONJ. Rather, COVID-19 appears to act synergistically with metabolic disorders, corticosteroid exposure, immune dysfunction, and local trauma, promoting vascular compromise and infectious bone injury.

Pathophysiology:

The development of post-COVID-19 osteonecrosis of the jaw (PC-ONJ) is multifactorial, involving COVID-19-associated vascular injury, immune dysregulation, medication effects, and pre-existing comorbidities. These factors may interact to impair bone perfusion, reduce tissue repair, and increase susceptibility to secondary infection. Moderate-to-severe COVID-19 can cause COVID-19-associated coagulopathy (CAC), a prothrombotic state characterized by systemic inflammation, endothelial dysfunction, and immunothrombosis [1,2]. Increased levels of IL-1β, IL-6, and TNF-α promote endothelial activation, tissue factor expression, thrombin production, platelet hyperactivity, neutrophil extracellular trap formation, and complement activation. These processes contribute to fibrin-rich microthrombi in small vessels [46,47]. In the jaws, obstruction of intraosseous microvessels may cause osteocyte ischemia, hypoxia, and bone microinfarction [7]. Reduced perfusion also impairs local immunity and healing, allowing mucosal injury and secondary microbial colonization. Corticosteroid exposure may further aggravate endothelial dysfunction and microcirculatory impairment [6,48]. ACE2 and TMPRSS2 are expressed in oral epithelial and salivary gland tissues, supporting the possibility of local SARS-CoV-2 interaction with these sites [49]. ACE2 also regulates the renin–angiotensin–aldosterone system by converting angiotensin II into angiotensin-(1–7), which supports vasodilation and endothelial stability. Viral interaction may reduce ACE2 availability, resulting in angiotensin II predominance, vasoconstriction, oxidative stress, inflammation, and endothelial dysfunction [50]. These changes may compromise periosteal and intraosseous perfusion, increasing susceptibility to osteocyte hypoxia and microinfarction [51]. Periodontal inflammation may further amplify local cytokine activity and delay mucosal healing [52,53]. However, direct evidence of persistent viral infection within jawbone remains limited; ACE2-related mechanisms are therefore considered potential contributors rather than confirmed direct causes [54].

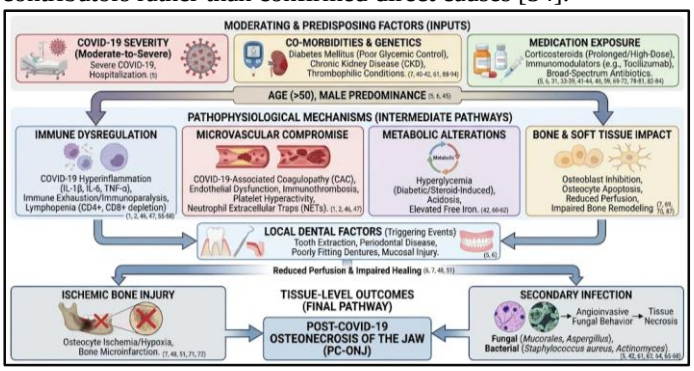


Figure-3: Risk factors and pathophysiology of post-COVID-19 osteonecrosis.

COVID-19 may produce an initial hyperinflammatory response followed by immune exhaustion or immunoparalysis. Lymphopenia, reduced CD4+ and CD8+ T-cell counts, and impaired cellular immunity may persist after clinical recovery [55–58]. Corticosteroids and other immunomodulatory treatments can further impair neutrophil function and host defense [59]. Hyperglycemia, acidosis, and elevated free iron may favor opportunistic fungal growth, particularly that of Mucorales [42,60–62]. Their angioinvasive behavior causes vascular thrombosis, ischemia, and tissue necrosis, especially in sinonasal and maxillofacial structures [42,63,64]. Other organisms, including Aspergillus, Staphylococcus aureus, and Actinomyces, may infect devitalized bone [5,65–68]. Systemic corticosteroids, including dexamethasone, may contribute to PC-ONJ through effects on bone metabolism, vascular integrity, immunity, and glucose regulation [36,69]. They inhibit osteoblast activity, promote osteocyte apoptosis, and alter osteoclast function [69,70]. Prolonged or high-dose exposure may also cause vascular dysfunction and bone infarction [71,72]. Steroid-induced hyperglycemia can worsen microvascular injury, delay healing, and increase fungal susceptibility [61,73–76]. Immunosuppression may also permit existing odontogenic infections to progress [59,77]. Tocilizumab may modify antimicrobial immune responses, although infection risk findings are inconsistent [78–81]. Broad-spectrum antibiotics can disrupt the microbiome and favor fungal overgrowth [82–84]. Hydroxychloroquine has been proposed as a possible modifying factor, but evidence does not establish it as a direct cause of osteonecrosis [85,86].

Diabetes, chronic kidney disease, and thrombophilic conditions may increase susceptibility to jaw necrosis by impairing vascular function, immunity, and bone repair [61,62,88–94]. Diabetes

promotes microangiopathy and impaired osteoblast function, while chronic kidney disease contributes to immune dysfunction and abnormal bone remodeling [7,76,87–95]. Antiphospholipid syndrome and antiangiogenic therapies may further compromise perfusion and tissue repair, although direct evidence linking them specifically to PC-ONJ remains limited [2,96]. Overall, COVID-19 is best regarded as a potential contributing factor rather than a solitary cause. Its vascular and immune effects may interact with medications and pre-existing conditions, increasing the likelihood of ischemic injury, secondary infection, and impaired jawbone healing.

Clinical Presentation and Spectrum of Post-COVID-19 Jaw Osteonecrosis

Post-COVID-19 osteonecrosis of the jaw (PC-ONJ) represents a spectrum of clinical and radiological manifestations rather than a single disease entity. Its presentation reflects overlapping ischemic, inflammatory, and infectious processes associated with SARS-CoV-2 infection and its treatment [5,84,97–99]. Common manifestations include persistent orofacial pain, swelling, tooth mobility, exposed or suspected necrotic bone, oroantral or oronasal fistulas, and oral ulcerations with delayed healing [5–7,100]. Notably, pain and other symptoms may precede visible bone exposure by weeks or months, making early recognition difficult [5,98]. Maxillary involvement predominates, accounting for more than 90% of reported cases, whereas mandibular involvement represents approximately 8–9% [5,6,99]. This distribution differs from conventional odontogenic osteomyelitis, which more commonly affects the mandible. The maxillary predominance may relate to its proximity to the paranasal sinuses, local vascular characteristics, and susceptibility to sinonasal disease extension [97,98]. Paranasal sinus involvement occurs in approximately 60% of cases and may indicate more extensive disease. Radiological findings include mucoperiosteal thickening, sinus wall erosion, and extension into adjacent structures [5–7]. Although less frequent, mandibular lesions may occur independently or alongside maxillary disease [6,85]. The interval between SARS-CoV-2 infection and jaw manifestations varies considerably. The reported mean is approximately 100 days, with cases occurring during active infection or more than 12–21 months after recovery [5,6]. Early presentations are frequently associated with COVID-19-associated mucormycosis (CAM) and may progress rapidly, involving the sinonasal region, orbit, or intracranial structures [66,100,101]. Conversely, late presentations often involve nonspecific dental symptoms that resemble routine odontogenic disease or chronic osteomyelitis [6,85,102]. A prolonged latency period does not necessarily indicate mild disease but may reflect gradual progression.

Delayed diagnosis is frequently reported because early symptoms may occur without bone exposure, while pain and tooth mobility can be attributed to common dental conditions. Early imaging may also lack specific findings [6,67,102]. Some patients receive repeated antibiotic courses for presumed bacterial osteomyelitis before developing bone sequestration or oro-sinus communications [6,85]. Dental extraction may also act as a local triggering event, with osteonecrosis becoming apparent months after COVID-19 [6,7]. Persistent pain, unexplained tooth mobility, and unusual mucosal lesions therefore warrant investigation in patients with a history of SARS-CoV-2 infection. Overall, the clinical spectrum ranges from slowly progressive dentoalveolar lesions to aggressive disease extending into the sinonasal, orbital, or cerebral regions [3,5,100]. A history of COVID-19 should be considered a contextual risk factor rather than definitive evidence of causation. Clinical assessment should integrate symptom characteristics, anatomical distribution, and disease chronology. Histopathological and microbiological investigations may help establish the underlying etiology, particularly in atypical or rapidly progressive cases [6,99]. Demographic characteristics, comorbidities, and COVID-19-related clinical factors should also inform individual risk assessment.

Diagnostic Challenges and Dilemmas

The diagnosis of post-COVID-19 oro-maxillofacial lesions remains challenging because different pathological conditions may produce overlapping clinical and radiological findings. Persistent facial pain, swelling, tooth mobility, exposed bone, fistulas, and sinonasal symptoms may occur in chronic osteomyelitis, medication-related osteonecrosis of the jaw (MRONJ), osteoradionecrosis (ORN), and invasive fungal infections [5,6,32,100]. Therefore, post-COVID-19 osteonecrosis of the jaw (PC-ONJ) should be considered a clinical descriptor rather than a definitive etiological diagnosis. Accurate classification requires integration of clinical examination, imaging, histopathology, and targeted microbiological investigations [5,7,104–107]. Imaging is essential for determining lesion extent and involvement of adjacent structures, but it rarely establishes the underlying etiology. Orthopantomography (OPG) is commonly used as an initial investigation to identify osteolysis and bone sequestration. However, it may be normal or inconclusive during early disease, particularly when lesions predominantly involve the bone marrow. Cone-beam computed tomography (CBCT) and computed tomography (CT) provide more detailed three-dimensional assessment of bone destruction and maxillary sinus involvement. Nevertheless, neither method reliably differentiates ischemic, bacterial, and fungal processes [7]. Magnetic resonance imaging (MRI) is useful for evaluating soft-tissue

involvement and extension toward the sinuses, orbit, and surrounding structures. However, imaging cannot replace biopsy when the diagnosis remains uncertain [7,67]. Biopsy and microbiological examination are central to etiological confirmation. Separate bacterial and fungal cultures may help distinguish secondary bacterial colonization from invasive fungal infection. Direct microscopic examination using potassium hydroxide, with or without calcofluor staining, can identify characteristic Mucorales hyphae. Histopathological examination provides further evidence by demonstrating fungal invasion, vascular thrombosis, and ischemic necrosis. Molecular techniques, including PCR, may assist when conventional investigations are inconclusive [7,104,105]. Interpreting results collectively is essential because tissue cultures, serum fungal markers, and histopathological findings may not always agree [104].

The differential diagnosis includes odontogenic osteomyelitis, complicated maxillary sinusitis, MRONJ, ORN, invasive fungal infection, and malignant disease. Relevant medical history should include antiresorptive or antiangiogenic medication use, previous cervicofacial radiotherapy, immunosuppressive treatment, and other potential etiological exposures. Biopsy is particularly important in extensive destructive lesions or persistent fistulas because it can establish infection and help exclude malignancy [7,104,106]. Interdisciplinary assessment is also necessary because patients may initially present to ear, nose, and throat (ENT) services with unilateral rhinorrhea, nasal congestion, cacosmia, or facial pain, or to oral and maxillofacial surgery (OMFS) services with dental pain, tooth mobility, and exposed bone. Coordinated evaluation helps identify the anatomical relationship between sinus disease and maxillary destruction. Management may require both surgical debridement or sequestrectomy and ENT procedures, including functional endoscopic sinus surgery [100,103–105]. A stepwise diagnostic approach can reduce misclassification. Warning signs include persistent or disproportionate facial pain, progressive swelling, sudden tooth mobility, persistent bone exposure, fistula formation, foul-smelling secretions, and failure to respond to empirical antibiotics [6,11,100]. Such findings warrant reassessment and advanced investigations rather than prolonged empirical treatment. Although universally validated diagnostic criteria for PC-ONJ remain unavailable, systematic exclusion of alternative causes through clinical history, imaging, histopathology, and microbiology provides a practical framework for diagnosis [6,48,49].

Management and Treatment Strategies

Management of post-COVID-19 osteonecrosis of the jaw (PC-ONJ) requires an etiologically guided approach that distinguishes COVID-associated mucormycosis (CAM) from non-fungal osteonecrosis. This distinction determines the need for antifungal therapy, antibiotics, surgical intervention, and systemic monitoring [7,105,106]. CAM is a medical and surgical emergency, with reported mortality of 40–80%. Liposomal amphotericin B (L-AmB), administered at 5–10 mg/kg/day, represents first-line treatment, with higher doses considered for cerebral involvement or rapid progression. Renal function and electrolyte levels require close monitoring. Delayed initiation of amphotericin B has been associated with increased mortality, emphasizing the importance of early treatment. Isavuconazole and posaconazole may serve as alternative or step-down therapies, particularly when amphotericin B causes renal toxicity or cannot be administered [106,107,110]. In contrast, antifungal therapy should not be routinely prescribed for non-fungal PC-ONJ without histopathological or microbiological evidence. These cases may respond to surgical debridement and perioperative antibiotics. Broad-spectrum antibiotics are indicated when bacterial superinfection is suspected, while 0.12–0.2% chlorhexidine rinses support local infection control [7,16]. Surgery is central to treatment, with its extent determined by the distribution of necrosis, underlying etiology, response to medical therapy, and general health status [24,106,111]. Sequestrectomy removes separated necrotic bone while preserving viable structures. Debridement and sequestrectomy are preferred for localized lesions, particularly in non-fungal disease. One reported series documented clinical resolution in 87% of patients with available follow-up following surgery and antibiotic therapy [11]. Extensive necrosis involving the palate, maxillary sinus, or adjacent structures may require partial or total maxillectomy and subsequent reconstruction. In CAM, adequate surgical removal of infected necrotic tissue is particularly important because of fungal angioinvasion and the potential for rapid progression [100,112]. Early intervention is associated with better outcomes, whereas delayed treatment may permit orbital or cerebral extension. Postoperative complications include oroantral communications, wound dehiscence, pain, edema, and persistent inflammation [11,100].

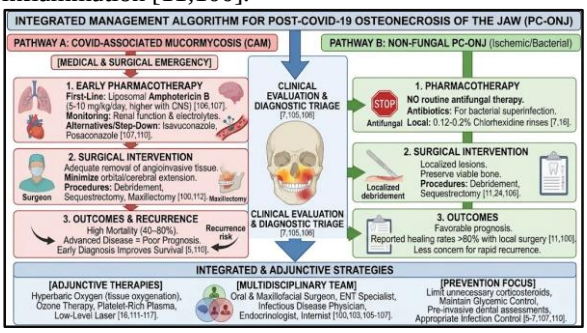


Figure-4: Management and Treatment of post-COVID-19 osteonecrosis of jaws.

Adjunctive therapies may support healing but cannot replace appropriate antifungal or antibacterial treatment and surgery. Hyperbaric oxygen therapy may improve tissue oxygenation and promote angiogenesis, although evidence specific to PC-ONJ remains limited [16,111–114]. Chlorhexidine rinses support oral hygiene, while ozone therapy, platelet-rich plasma, and low-level laser therapy have been proposed for antimicrobial activity, tissue regeneration, and postoperative healing. Their application requires further investigation [115–117]. Effective management requires collaboration among oral and maxillofacial surgeons, ENT specialists, infectious disease physicians, endocrinologists, and internists. This coordination supports surgical planning, sinonasal disease control, antimicrobial selection, toxicity monitoring, and correction of metabolic abnormalities [100,103,105–107]. Prevention focuses on limiting unnecessary corticosteroid exposure, maintaining glycemic control, performing dental assessment before invasive procedures in high-risk patients, and monitoring persistent post-COVID dental symptoms. Appropriate infection-control practices in healthcare settings may also reduce mucormycosis risk [5–7,105,107,110]. Treatment outcomes differ substantially between CAM and non-fungal PC-ONJ. CAM carries higher mortality, particularly with orbital or cerebral extension, whereas non-fungal cases generally have more favorable outcomes, with reported healing rates exceeding 80% following local surgery in some series [6,7,100,112]. Recurrence is more concerning in CAM and may be associated with incomplete debridement, premature discontinuation of antifungal therapy, and poor metabolic control [105,106]. Advanced age, uncontrolled diabetes, prolonged corticosteroid exposure, extensive disease, and delayed diagnosis are associated with poorer prognosis. Early diagnosis, limited necrosis, metabolic control, and coordinated multidisciplinary treatment improve the likelihood of recovery [5,11,100,110].

Conclusion:

Post-COVID-19 osteonecrosis of the jaw represents a complex clinical condition with diverse presentations and potentially multiple underlying mechanisms. Its recognition requires careful assessment of clinical history, risk factors, imaging findings, and histopathological and microbiological evidence. Distinguishing non-fungal osteonecrosis from COVID-associated mucormycosis is essential because their treatment approaches and prognoses differ. CAM requires urgent antifungal therapy and timely surgical intervention, while non-fungal lesions require individualized management based on disease severity and evidence of secondary infection. Uncontrolled diabetes, prolonged corticosteroid exposure, immunosuppression, and delayed diagnosis may contribute to disease progression and poor outcomes. Coordinated care involving oral and maxillofacial surgeons, otolaryngologists, infectious disease specialists, and physicians is therefore important. Further prospective studies are needed to establish standardized diagnostic criteria, clarify pathogenic mechanisms, identify reliable predictors of disease progression, and evaluate treatment effectiveness. Improved awareness and early intervention may reduce complications and improve patient outcomes.

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