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REVIEW

Dentistry and rheumatology collaboration: dental health, treatment and measures for osteonecrosis of jaw for patients with vasculitis

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ABSTRACT

The relation between rheumatology and dentistry has increasing clinical importance, particularly in patients with systemic autoimmune diseases such as rheumatologic disorders and vasculitis. Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of periodontal supporting tissues, occurring from a dysbiotic shift within the oral microbiota. Although the primary etiological factor of periodontal disease is bacterial plaque, the main factor causing breakdown in the periodontium is the host-mediated immunoinflammatory response. Periodontal diseases can have both direct and indirect impacts on overall systemic health through possible remote effects of the inflammatory response caused by bacterial infection of the periodontium, and serving as a risk factor for systemic diseases or conditions affecting general health. Oral lesions may develop in patients with vasculitis during the course of the disease, and oral findings may even be the first clinical findings before the diagnosis. Bone-modifying agents (BMAs) such as bisphosphonates, used to prevent osteoporosis associated with various autoimmune and immune-mediated inflammatory disease, can predispose individuals to complications affecting bone metabolism and oral health, including medication-related osteonecrosis of the jaw (MRONJ). In such cases, effective prevention, early diagnosis and multidisciplinary management are essential to reduce morbidity and maintain oral function.

The present review aims to evaluate the potential interactions between periodontitis and rheumatological diseases; to assess the etiological/pathological basis of these diseases and the multidisciplinary approaches between periodontal and rheumatologic disciplines in promoting oral health and reducing the risk of osteonecrosis in patients with vasculitis.

Keywords: Periodontal diseases, rheumatic diseases, rheumatoid arthritis, vasculitis, autoimmunity.

INTRODUCTION

Periodontal diseases are a group of conditions that develop through an inflammatory process initiated by bacterial pathogens within complex polymicrobial interactions in the oral microbiome. In the United States, approximately 47% of adults aged 30 years and older (around 65 million adults) have periodontitis: 30% with moderate, 8.5% with severe, and 8.7% with mild periodontitis. Periodontal infections lead to substantial healthcare costs related to their local effects and are also associated with numerous systemic diseases [1]. Environmental, physical, social, and host-related factors can influence and modify the disease course in various ways. Certain systemic conditions may also affect the onset and progression of gingivitis and periodontitis. Systemic disorders that impair the function of neutrophils, monocytes, macrophages, and lymphocytes cause alterations in the production or activity of host inflammatory mediators. Clinically, these alterations may manifest as an earlier onset or a faster progression of periodontal destruction than would occur in their absence [2].

For many years, periodontal disease was regarded as an infectious disease; however, since the 1960s, autoimmune mechanisms have been demonstrated as determinant factors in addition to the host response to microorganisms responsible for infection. The presence of anti-collagen antibodies produced by plasma cells within the periodontal tissues of patients with periodontitis has been demonstrated [3]. Based on this, it has been suggested that a disease-causing destruction in periodontal tissues may involve a possible autoimmune process and influence other rheumatologic–immunologic mechanisms as well [4].

In recent years, numerous scientific studies have shown that periodontal health can have both direct and indirect effects on overall systemic health. The potential effects of inflammatory periodontal diseases on multiple organ systems can be evaluated under two main aspects: (1) the possible remote effects of the inflammatory response elicited by bacterial infection of the periodontium, and (2) the degree to which periodontal infection serves as a risk factor for systemic diseases or conditions affecting general health [2]. The epidemiologic relationship between periodontal diseases and various rheumatologic diseases has been demonstrated by many clinical studies [5].

The association between periodontitis and other systemic and rheumatologic diseases has been recognized since the early 20th century, particularly during the period dominated by the "focal infection theory." During that time, dental treatments were largely limited to tooth extractions. There are also early reports suggesting that non-extraction treatment approaches for periodontal disease could alleviate rheumatologic symptoms. One case report described a 45-year-old male patient presenting with severe rheumatoid arthritis, difficulty walking, and stiffness in the knee joints. Prior to dental intervention, he had received streptococcal vaccine therapy, but despite having apparently healthy teeth with no visible infection, his arthritis did not improve. A detailed periodontal examination revealed hard, brown calculus surrounding the tooth roots and periodontal pockets. The patient was treated with a protocol involving complete removal of calculus, root surface polishing, and ionization with zinc ions at each session. After treatment, the gingival tissues completely healed, and within three months, marked improvement in arthritis symptoms was observed. Ten months later, the patient was able to walk unaided [6]. Although this report presents only a single case and was published during a period when scientific journals lacked today's rigorous peer review processes, it remains noteworthy for illustrating the historical context of the relationship between periodontal and rheumatologic diseases.

To better understand the effects of periodontal diseases on rheumatologic conditions—and to clarify the role of dental practitioners in managing patients with rheumatologic diseases—it is essential to review the general characteristics of periodontal diseases and their treatment approaches.

Periodontal Diseases

Gingivitis presents inflammation limited to the soft tissue of the gingival epithelium and connective tissue, without the attachment loss or apical migration of the junctional epithelium observed in periodontitis. Depending on the duration of infection and etiology, the most common form is chronic plaque-induced gingivitis. The transition from gingivitis to periodontitis is a multifactorial process beginning with biofilm accumulation on tooth surfaces and progressing to tissue destruction due to dysregulation of the host immune response. Initially, dental plaque triggers a local inflammatory response characterized by increased vascular permeability, edema, and neutrophil infiltration. If plaque accumulation persists, the adaptive immune system becomes activated, dominated by T and B lymphocytes and plasma cells. At this stage, gingivitis develops, which is reversible with appropriate intervention.

If left untreated, inflammation activates more complex mechanisms, leading to periodontitis. Persistent microbial stimulation causes macrophages and T cells to release IL-1β, TNF-α, IL-6, PGE_2, and matrix metalloproteinases (MMPs), mediating connective tissue and bone destruction. Additionally, osteoclast activation through the RANKL pathway results in alveolar bone resorption [7].

Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of microorganisms, resulting in progressive destruction of the periodontal ligament and

alveolar bone, accompanied by increased probing depth, gingival recession, or both." The principal clinical feature distinguishing periodontitis from gingivitis is clinically detectable attachment loss due to inflammatory destruction of the periodontal ligament and alveolar bone. This is often accompanied by periodontal pocket formation and changes in the density and height of the subjacent alveolar bone. Persistent bleeding on probing during sequential visits is a reliable indicator of inflammation and of increased risk for future attachment loss at the bleeding site. The attachment loss associated with periodontitis may occur in a cyclic pattern, progressing either continuously or in episodic bursts of disease activity [8].

The 2017 Classification of Periodontal and Peri-implant Diseases introduced a new staging and grading system, defining four stages of disease (1–4) and three progression rates or risk levels (A–B–C). The classification considers parameters such as clinical attachment loss, pocket depth, percentage of alveolar bone loss, and the number of teeth lost due to periodontal disease. Grading is based on annual attachment loss, bone loss-to-age ratio, and systemic risk factors such as smoking and HbA1c levels [9].

In contemporary dentistry, peri-implant diseases—inflammatory conditions around dental implants—share similar features with periodontal disease. These are categorized as peri-implant mucositis and peri-implantitis, as defined by the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions. Peri-implant mucositis refers to an inflammatory lesion confined to the peri-implant mucosa surrounding an osseointegrated implant, without accompanying bone loss. Peri-implantitis is characterized by inflammation in the peri-implant mucosa combined with progressive loss of supporting bone [9].

Periodontitis: Effects on Dysbiosis and Host Immune Response

Periodontitis is a disease characterized by progressive destruction of the periodontal tissues resulting from dysbiosis within the oral microbiota. In the pathogenesis of the disease, a crucial role is attributed not only to the anaerobic, Gram-negative bacteria known as the "red complex"—*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*—but also to *Aggregatibacter actinomycetemcomitans*. These microorganisms disturb the microbial balance essential for maintaining periodontal health, leading to a microbial shift that promotes pathogenic dominance. When the red complex bacteria establish stable colonization in the gingival sulcus—the natural space between the tooth and the gingiva—the host's innate immune system is activated.

However, these pathogens embedded in the dysbiotic biofilm develop resistance to host defense mechanisms such as phagocytosis, antimicrobial proteins and peptides, and reactive oxygen species, rendering their elimination extremely difficult. As a result, a chronic inflammatory process is sustained within the periodontal tissues [1].

In this process, tissue destruction is caused primarily not by the bacteria themselves, but by the dysregulated immune response of the host. Neutrophil infiltration, cytokine release (e.g., IL-1β, TNF-α, IL-6), and activation of matrix metalloproteinases (MMPs) contribute to the breakdown of connective tissue and resorption of alveolar bone. Thus, an immune response initially aimed at protection becomes pathogenic and self-destructive over time.

Although periodontitis manifests as a localized inflammatory disease, its effects extend beyond the oral cavity. Hyperactivated neutrophils and elevated levels of inflammatory mediators (such as cytokines and C-reactive protein) originating from periodontal pockets can enter the systemic circulation. This indicates that periodontitis should not be viewed solely as a local disease but as a pathology contributing to systemic inflammatory burden [10].

To quantify the systemic impact of periodontitis, researchers have proposed correlating it with the periodontal inflamed surface area (PISA)—the total inflamed epithelial area in the periodontal pockets. Based on this analysis, the inflamed gingival surface area has been calculated as approximately: 0.3 cm^2 in healthy individuals, 10 cm^2 in localized periodontitis, and 37 cm^2 in generalized severe periodontitis [11]. This model provides a measurable index of the systemic inflammatory load associated with periodontal disease.

Mechanisms of the Effect of Periodontitis on Autoimmunity

In the oral cavity, as in other mucosal systems exposed to the external environment, the immune system is continuously challenged by signals extending beyond simple commensal–epithelial interactions. This ongoing exposure contributes to immune system "education" through mechanisms that remain only partially understood. However, disruption of these localized responses is associated with a predisposition to tissue-specific autoimmune diseases.

Periodontitis serves as a prototype of such conditions, reflecting both local and systemic inflammatory processes and the activation of autoimmunity. It demonstrates a dysregulation of immune homeostasis that extends beyond local tissue pathology. Accordingly, the modern concept of periodontal disease has evolved: it is no longer attributed to a single pathogen but rather to polymicrobial dysbiotic communities that disturb tissue homeostasis and normal immune responses [12].

Animal studies have shown that *P. gingivalis*, recognized as a "keystone pathogen," can increase the overall virulence of the microbial community even when present in very low abundance (below 1%). Interactions between this bacterium and normally commensal microorganisms promote synergy and a transition toward pathogenicity, perpetuating dysbiosis. The resulting dysbiotic community sustains chronic inflammation and displays "inflammophilic" characteristics—bacteria thrive on tissue breakdown products as nutrient sources—further amplifying the cycle of destruction [1, 12]. From this perspective, periodontitis currently involves the dysbiosis of oral microbiota driven by inflammophilic bacteria. This process leads to impaired resolution of inflammation and failure to adequately regulate immune responses. Tissue destruction in periodontitis arises directly from immune activation due to the bidirectional imbalance between the microbiome and host inflammatory mechanisms. This dysregulation triggers both local and systemic autoimmune responses through multiple mechanisms, including: (A) Overproduction of autoantigens; (B) Microbial translocation; (C) Molecular mimicry; (D) Superantigen activation; (E) Dysregulation of immune checkpoints; (F) Bystander activation; (G) Dysregulation of Toll-like receptors (TLRs); (H) Excessive cytokine production; (I) Epitope spreading; (J) Complementarity of autoantigen [4].

Among autoimmune and rheumatic diseases influenced by periodontitis, the strongest evidence exists for rheumatoid arthritis (RA). Periodontal inflammation—particularly the role of *Porphyromonas gingivalis* in the citrullination process—has been implicated in the pathogenesis of RA. Additionally, increased prevalence of periodontitis has been reported in systemic lupus erythematosus (SLE), with overlapping inflammatory pathways. Periodontal disease is also observed more frequently in patients with juvenile idiopathic arthritis (JIA), ankylosing spondylitis, and other connective tissue disorders, and it may correlate with disease activity [13].

Periodontitis–Rheumatoid Arthritis Relationship

Over the past decade, a growing body of evidence has left little doubt that periodontitis and rheumatoid arthritis (RA) are closely interrelated. This association cannot be explained solely by shared pathogenic mechanisms or by overlapping environmental and genetic risk factors. Large cohort studies have demonstrated that periodontitis often precedes the onset of RA, and that individuals who develop RA exhibit a positive correlation between periodontitis and serum ACPA (anti-citrullinated protein antibody) levels. These findings provide strong support for a causal relationship between the two diseases. According to this model, the chronically inflamed periodontium serves as the site where immune tolerance to citrullinated epitopes is broken, initiating ACPA production. This theory has been validated in both animal and human models of periodontitis and RA and aligns with the paradigm suggesting that ACPAs are produced at mucosal surfaces years before clinical RA symptoms emerge [10].

Under inflammatory conditions, the mechanisms leading to hyper-citrullination occur predominantly at mucosal sites. In chronic inflammation of the periodontium, nearly all mechanisms contributing to the generation of citrullinated epitopes are triggered by periodontal pathogens. Thus, periodontal pathogens are considered direct initiators of autoimmune reactions that later give

rise to diseases such as RA. The mechanistic role of periodontitis and periodontal pathogens in RA development has been supported by case–control studies showing ACPA production at other mucosal surfaces, including the lungs and intestines. Collectively, these findings reveal a highly interconnected network of interactions capable of initiating the onset of RA [10].

Courbon et al. [14] investigated the specific role of *P. gingivalis* in the development of periodontitis and subsequent arthritis. In their experiment, rats were orally exposed for one month to either *P. gingivalis, Prevotella intermedia*, or a control gel, and monitored for eight months. Periodontitis development was assessed using serological analyses, gingival inflammation scores, and micro-CT imaging, while arthritis development was evaluated by measuring proinflammatory markers, anti-CCP, ACPA levels, and by histological and μCT analysis of ankle joints. The results showed that periodontitis developed exclusively in the *P. gingivalis* group, beginning one month after exposure. Both joint inflammation and systemic inflammation were detected only in this group at the 4th and 8th months. By the eighth month, ankle joints exhibited infiltration of inflammatory cells, cortical erosions, and overall bone loss. Additionally, anti-CCP2 antibody levels were found to correlate with both local and systemic bone loss.

Another study assessing citrullinated histones in inflamed periodontal tissue and sera of patients with RA and periodontitis demonstrated the presence of citrullinated histone H3 in periodontal tissue samples. Furthermore, sera from RA patients contained higher levels of autoantibodies against citrullinated histone H3 compared to healthy controls and periodontitis patients. These findings indicate that periodontitis contributes to the formation of antigens targeted by ACPAs [15].

In another in vivo mouse model, the arthritogenic effect of lipopolysaccharide (LPS) in periodontal disease was investigated. Periodontitis was induced in CD1 mice by injecting either 10 ng or 50 ng of LPS into the maxillary mucosa. Control mice were either untreated or injected with LPS at the tail. Mice receiving 50 ng LPS developed ankle swelling and inflammation after the fifth injection, which progressed until the end of the experiment. Micro-CT and histologic analyses revealed alveolar bone resorption, vascular proliferation, widening of joint space, leukocyte infiltration, synovial proliferation, and mild cartilage/bone destruction. Furthermore, increases in serum cytokine and ACPA levels were observed. Importantly, no arthritic changes developed in mice where LPS was injected in the tail, demonstrating that RA-like symptoms occurred only when LPS induced periodontitis locally [16].

A large-scale case–control study involving over 600 participants examined the prevalence of periodontitis among RA patients. It found that periodontitis was significantly more common in RA patients compared to controls and that the percentage of sites with probing depth ≥5 mm was markedly higher among RA patients [17]. Another cross-sectional study analyzed active matrix metalloproteinase-8 (aMMP-8) levels and periodontal bacterial profiles in gingival crevicular fluid of RA patients. Despite comparable periodontal and bacterial findings between the groups, RA patients exhibited significantly higher aMMP-8 levels correlated with the severity of periodontitis, suggesting a modulatory effect of RA on host immune response [18].

Epidemiological and cross-sectional data support a bidirectional relationship between periodontitis and RA. Numerous studies have evaluated how periodontal treatment influences RA disease activity and severity [10]. Meta-analyses of these studies confirm that periodontitis should be considered a modifiable risk factor for rheumatoid arthritis [5]. A clinical study evaluating the efficacy of non-surgical periodontal therapy in RA patients with periodontitis found that the treatment group exhibited significant reductions in DAS28-CRP, serum IgG levels against *P. gingivalis* hemin-binding protein (HBP35), and serum citrulline levels after eight weeks compared with untreated controls. Serum IgG levels against *P. gingivalis* HBP35 were positively correlated with anti-cyclic citrullinated peptide (anti-CCP) antibody levels, and a similar correlation was observed between *P. gingivalis*-specific IgG and rheumatoid factor (RF) levels [19].

Likewise, a recent study reported that in RA patients with periodontitis, scaling and root planing (SRP) significantly reduced DAS28-CRP, disease activity classification, ESR, and serum ACPA levels, demonstrating that non-surgical periodontal therapy can effectively reduce RA disease severity [20]. A simple, non-invasive, and cost-effective,

and procedure with predictable outcomes such as periodontal treatment can therefore contribute to lowering both local and systemic inflammatory load, potentially reducing the need for systemic pharmacologic therapy in RA and minimizing the risk of life-threatening complications, particularly cardiovascular events. Chemical mouthrinses containing various antimicrobial compounds and photodynamic therapy are currently being tested as adjuvants to SRP. Analyses of existing studies indicate that periodontal therapy exerts a more significant effect on reducing clinical disease activity indices than on ESR and CRP, as the latter are influenced by multiple factors—especially infections—which are more frequent in rheumatic patients chronically treated with glucocorticoids and immunosuppressants. The collective evidence strongly supports that routine periodontal examination should be incorporated into RA management guidelines, emphasizing early detection and treatment of periodontitis [5, 13].

Vasculitis and Periodontal Diseases

Vasculitis are a heterogeneous group of diseases characterized by chronic inflammation of blood vessels, which can lead to multi-organ involvement and serious systemic complications. According to the 1994 classification, vasculitis are primarily categorized based on the size of the predominantly affected vessels into four main groups: 1) Large-vessel vasculitis (e.g., giant cell arteritis), 2) Medium-vessel vasculitis (e.g., Kawasaki disease), 3) Small-vessel vasculitis—including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAVs), variable-vessel vasculitis (e.g. Behçet's disease) [21]. Although the etiopathogenesis of AAVs has not been fully elucidated, it is hypothesized that the formation of anti-neutrophil cytoplasmic antibodies triggers this autoimmune response. ANCAs target the cytoplasmic granules of neutrophils, initiating a systemic inflammatory cascade. Clinical symptoms vary considerably depending on the vascular bed involved, but the respiratory and renal systems are most commonly affected. In addition to organ-specific manifestations, patients frequently exhibit non-specific systemic signs of inflammation such as fever, headache, fatigue, loss of appetite, myalgia, arthralgia, constipation, and weight loss [21, 22].

Oral Manifestations in Vasculitis (Selected Entities)

Granulomatosis with polyangiitis (GPA) is a necrotizing systemic vasculitis primarily affecting the upper and lower respiratory tracts, but it may also involve the kidneys, skin, and nervous system. In most patients, the disease initially presents with head and neck symptoms [21]. The nasal septum, paranasal sinuses, ocular structures, larynx, ear, and oral cavity may all be affected. Approximately 10% of GPA patients develop oral lesions during the course of disease, and in 2% of cases, oral manifestations may be the first clinical sign before diagnosis. Moreover, oral lesions can serve as indicators of disease relapse or exacerbation. One of the most characteristic oral findings of GPA is gingival enlargement, classically described as "strawberry gingivitis." In this condition, the gingiva appears edematous, erythematous, and painful, with superficial petechiae giving the mucosa a strawberry-like appearance. Histopathologically, affected tissues may show fibrinoid necrosis of vessel walls, predominantly neutrophilic and non-specific lymphocytic infiltrates, and granuloma formation—although these features are not always present and are not pathognomonic. Diagnosis is based on clinical findings, systemic evaluation, and the presence of ANCA. Direct immunofluorescence may reveal IgM and/or C3 deposits surrounding vessel walls [21, 22].

Microscopic Polyangiitis (MPA)

Microscopic polyangiitis (MPA) is primarily characterized by a pulmonary–renal syndrome and differs from GPA by the absence of granuloma formation and eosinophilia [20]. Oral involvement is extremely rare and has been reported only in a few cases. In a cohort of ten female patients, oral ulcers were documented in two cases as part of extra-renal involvement. In one patient, gingival enlargement was observed and constituted the first clinical clue leading to the diagnosis of MPA following oral lesion evaluation. Histopathological features include fibrinoid necrosis of vessel walls with dense neutrophilic infiltration, sometimes accompanied by non-specific lymphocytic infiltrates. Direct immunofluorescence findings may be negative or show limited IgM and/or C3 deposition [21].

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Eosinophilic granulomatosis with polyangiitis (EGPA) is a type of vasculitis characterized by eosinophil-rich necrotizing inflammation, primarily affecting the lungs, and is typically associated with asthma and atopic conditions [21]. Oral involvement in EGPA is extremely rare, with only a few reports of ulcerative lesions. Some cases describe painful palatal ulcers developing about a week before the appearance of cutaneous lesions. Throughout the disease course, multiple small ulcers resembling aphthous stomatitis have been reported. The overall prevalence of oral ulcers among EGPA patients is estimated at around 2%, suggesting that such lesions may represent part of the broader clinical spectrum of EGPA. Histopathological examination shows vasculitis with fibrinoid necrosis and, occasionally, granulomatous lesions. A diagnostic hallmark is the presence of numerous eosinophils within the inflammatory infiltrate, accompanied by neutrophils, macrophages, and lymphocytes. Direct immunofluorescence may show IgM and/or C3 deposits in the vessel walls [22].

Medication-Related Osteonecrosis of the Jaws (MRONJ) And Rheumatic Diseases

Autoimmune and immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are associated with an increased risk of osteoporosis, falls, and fractures due to chronic inflammation, pharmacologic therapies, and reduced mobility. These conditions are commonly managed with conventional and biologic disease-modifying antirheumatic drugs (cDMARDs and bDMARDs) in combination with glucocorticoids. While these drugs effectively control disease activity, they can contribute to bone loss and heightened infection risk. To prevent osteoporosis, bone-modifying agents (BMAs) such as bisphosphonates and denosumab are widely prescribed in this patient group. However, long-term use of BMAs has been strongly associated with medication-related osteonecrosis of the jaws (MRONJ)—a rare but serious adverse effect, typically occurring after invasive dental procedures. Accordingly, the interaction among autoimmune disease, immunosuppressive therapy, bone-modifying agents, and oral health constitutes a critical clinical interface for both rheumatology and dentistry [23].

Definition and Pathophysiology

Medication-related osteonecrosis of the jaws (MRONJ), also referred to as osteonecrosis of the jaw (ONJ), is characterized by one or more necrotic bone lesions in the maxillofacial region, visible through intraoral or extraoral fistulae, and persisting over time. Although uncommon, it represents a serious clinical condition with potentially chronic consequences [24].

The diagnostic criteria for MRONJ include [25]: 1) Current or previous treatment with antiresorptive agents alone or in combination with immune modulators or anti-angiogenic drugs; 2) Exposed bone or bone that can be probed through intraoral or extraoral fistulae in the maxillofacial region persisting for at least 8 weeks; 3) No history of radiation therapy to the jaws or metastatic disease involving the jaws.

Among medications implicated in MRONJ, bisphosphonates (particularly intravenous forms) and denosumab are the most frequently associated drug classes. Other agents such as bevacizumab, romosozumab, and various tyrosine kinase inhibitors have also been linked to MRONJ in published case reports [25].

The pathophysiology of MRONJ primarily involves three mechanisms: 1) Suppression of bone remodeling, 2) Inflammation and/or infection, and 3) Impaired vascularization. Antiresorptive agents—including bisphosphonates and denosumab—exert direct effects on osteoclast formation, differentiation, and function. Because many teeth requiring extraction present with pre-existing periapical and/or periodontal infections, local inflammation and infection are major contributors in MRONJ pathogenesis. Additionally, bisphosphonates have been shown in vitro and in vivo to directly inhibit angiogenesis. Animal models demonstrate reduced vascularity and decreased micro vessel density in early bone healing phases within MRONJ lesions. Compromised angiogenesis following tooth extraction delays alveolar socket healing and increases the risk of secondary infection [24, 25].

Clinical Manifestations of MRONJ

Clinical manifestations of MRONJ typically begin with localized inflammation and progress to more pronounced soft and hard tissue changes.

In the early stages, patients may exhibit mucosal inflammation, non-healing extraction sockets, and sensory disturbances such as lip numbness. As the disease advances, purulent discharge, soft-tissue swelling, spontaneous loss of bone sequestra, tooth or implant mobility, severe dental pain, and trismus may develop. The presence of these findings indicates progression of osteonecrosis and the need for early intervention.

In advanced stages, both soft and hard tissues are affected by infection and necrosis. Clinically, abscess formation, bone exposure, intraoral or cutaneous fistulae, and nasal discharge may be observed. These conditions are often accompanied by halitosis and jaw pain originating from necrotic bone. In the late phases of MRONJ, pathologic mandibular fracture or segmental mobility, mandibular deformity, and widened periodontal ligament space may occur, leading to increased tooth mobility. These severe signs reflect the progressive and destructive nature of MRONJ and underscore the importance of early diagnosis, preventive strategies, and multidisciplinary treatment planning [24-26].

Risk Factors for MRONJ

Pharmacologic agents and therapeutic indications play a major role in MRONJ risk (Table 1).

For tyrosine kinase inhibitors (e.g., sunitinib), VEGF inhibitors (e.g., bevacizumab), fusion proteins (e.g., aflibercept), mTOR inhibitors (e.g., everolimus), and TNF-α inhibitors, methotrexate, and corticosteroids, MRONJ has been reported, though not consistently defined as a risk when used alone.

Local factors contributing to MRONJ include: dentoalveolar surgical procedures (e.g., extractions, implant surgery); poor oral hygiene or inadequate professional maintenance; periodontitis or peri-implantitis; dental trauma; and anatomical site (mandible carries approximately 3× greater risk). Demographic and systemic factors include smoking (×3 risk), diabetes mellitus, and hemoglobin levels <10 g/dL [24, 25]

Table 1. Risk of MRONJ for different medications and indications [25]

Drug / Indication	Reported MRONJ Risk
Zoledronate (IV) – Cancer therapy	<5%
Zoledronate – Osteoporosis therapy	<0.02%
Denosumab – Cancer therapy	6.5%
Denosumab – Osteoporosis therapy	0.04–0.3%
Alendronate	<0.05%
Romosozumab (osteoporosis)	0.03–0.05%

The most critical determinant of MRONJ risk is the dosage and frequency of bone-modifying/antiresorptive agents. High-dose (HD) intravenous bisphosphonates (e.g., 4 mg monthly zoledronate) and subcutaneous denosumab at oncologic doses (120 mg monthly) represent the highest risk. In contrast, low-dose (LD) antiresorptive therapies for osteoporosis (oral or parenteral BP, or 60 mg denosumab every 6 months) carry significantly lower risk. Patients receiving high-dose BMAs for multiple myeloma (MM) or bone metastases (BM) constitute the highest-risk group, with MRONJ incidence and prevalence ranging between 1% and >20%. Recent systematic reviews indicate that zoledronic acid carries a higher MRONJ risk than other bisphosphonates (e.g., pamidronate, ibandronate), and denosumab confers an even higher risk than zoledronic acid. MRONJ risk appears to increase with treatment duration. Kaplan–Meier survival analyses in MM/BM patients show a progressive rise in MRONJ risk with longer treatment years. It remains unclear whether treatment duration (drug exposure) or observation period (patient survival) is the more dominant factor; however, prolonged therapy and extended survival can raise cumulative incidence up to 30% over 8 years in certain metastatic cancer subgroups [25, 26]

Preventive Strategies and Dental Management in MRONJ Patients

Although recent updates have introduced new treatment strategies for MRONJ, predictability of treatment outcomes remains limited due to local factors and patient comorbidities. Therefore, preventive dental management is of paramount importance. The Italian position paper (SIPMO–SICMF, 2024) provided structured recommendations for the prevention and management of MRONJ, categorizing patients according to the dose and regimen of antiresorptive therapy and defining practical guidance for dental treatment planning [26] (Table 2).

Table 2. Antiresorptive Dose Groups and Subcategories [26]

Antiresorptive Dose Group	Definition
Low Dose (LD-AR)	R_0: Planned LD-AR therapy not yet initiated, or <3 years of LD-AR use without additional systemic risk factors. R_x: Ongoing LD-AR therapy >3 years, or <3 years with additional risk factors (i.e., concurrent systemic risk factors in patients on <3 years of LD-BMA therapy).
High Dose (HD-AR)	R_0: Planned HD-AR therapy not yet initiated. R_+: Ongoing HD-AR therapy without additional systemic risk factors. R_{++}: Ongoing HD-AR therapy with additional systemic risk factors, or in combination with anti-angiogenic drugs.

Table 3. Preventive Dental Care Strategies for MRONJ [25]

Stage	Strategies
During Antiresorptive Therapy (Non-malignant Disease)	- No changes to standard operative plans are required for most patients. - Evaluate medication type and duration, comorbidities, concomitant drugs (esp. chemotherapy, steroids, anti-angiogenics), baseline infection/inflammation, and extent of surgery. - Consider individualized "drug holidays." - Bone turnover markers are not reliable tools for MRONJ risk assessment.
During Antiresorptive / Targeted Therapy (Malignant Disease)	- Inform patients that MRONJ risk is higher in malignancy-associated AR therapy. - Educate patients on regular dental maintenance and preventive oral hygiene. - Avoid dentoalveolar surgery when possible. - Consider conservative techniques to avoid extractions. - Dental implants are contraindicated. - Discuss drug holidays when appropriate.

Table 4. Dental Treatment Recommendations According to BMA Dose Category [25]

Dental Treatment	High-Dose BMA (HD-BMA) – R_+ and R_{++}	Low-Dose BMA (LD-BMA) – R_x
Non-surgical Procedures		
Restorative Dentistry	Indicated	Indicated
Endodontic Treatment	Indicated	Indicated
Orthodontic Treatment	Conditional	Conditional
Periodontal Therapy	Indicated	Indicated
Prosthetic Rehabilitation	Conditional	Conditional
Surgical Procedures		
Dentoalveolar Surgery	Indicated	Indicated
Tooth Extraction	Indicated	Indicated
Pre-implant Bone Augmentation	Contraindicated	Conditional
Dental Implant Surgery	Contraindicated	Conditional
Periodontal Surgery	Indicated	Indicated
Endodontic Surgery	Indicated	Indicated

Dental interventions are classified as either necessary/emergency procedures—those aimed at eliminating infectious foci (e.g., pulpitis, pericoronitis, periapical or periodontal abscesses, peri-implantitis, dental trauma, pain, or tissue damage caused by prostheses) or elective procedures such as esthetic restorations, orthodontic treatments, elective periodontal or endodontic procedures, and prosthetic rehabilitations [24, 25] (Table 3).

The SIPMO–SICMF Expert Panel proposed a traffic-light classification system to help clinicians balance the risk–benefit ratio of dental procedures in patients receiving bisphosphonates or other BMAs. Treatments are categorized as: Indicated (Green light): all essential and emergency procedures not associated with an increased MRONJ risk; Conditional (Yellow light): elective procedures with uncertain MRONJ risk, permissible under controlled conditions; Contraindicated (Red light): elective

surgical interventions with clearly unfavorable risk–benefit profiles (Table 4).

Drug Holiday Practices

In patients without clinical signs of MRONJ, the concept of a prophylactic "drug holiday"—temporary suspension of bisphosphonate therapy prior to oral surgical procedures—has been proposed over the past two decades for patients with osteoporosis or multiple myeloma, in an effort to enhance wound healing. However, the duration of the drug holiday varies widely in the literature, ranging from a few weeks to several months, depending on published protocols. Evidence from both clinical and animal studies does not provide strong support for the routine use of drug holidays to prevent MRONJ. Thus, such interruptions are considered theoretical measures, based on pharmacokinetic reasoning rather than solid empirical data [25, 27].

Given current evidence, the SIPMO–SICMF Expert Panel advises that prophylactic suspension of denosumab should be approached cautiously, especially in patients at elevated MRONJ risk. Treatment planning should be individualized, depending on the type of pharmacologic agent and dosage regimen (Table 5).

Therapeutic and Preventive Outlook

Conservative and preventive therapy constitutes the cornerstone of MRONJ management and is applicable in the vast majority of cases. For refractory MRONJ cases unresponsive to conservative treatment, surgical intervention remains the primary approach. Teriparatide (TPTD) has emerged as a potentially promising conservative option in osteoporotic patients, though its efficacy—as well as that of other proposed therapies—requires further validation [24, 28].

In rheumatology, newer-generation DMARDs are increasingly used and, unlike glucocorticoids, do not negatively affect bone metabolism, potentially contributing to a lower prevalence of drug-induced osteoporosis. Moreover, the targeted anti-inflammatory effects of these new biologics may indirectly reduce MRONJ risk. However, risks associated with older therapies persist, and the long-term safety profiles of newer drugs must continue to be evaluated.

The overall benefits of antiresorptive therapy far outweigh the potential risks, offering substantial reductions in skeletal-related events among oncology patients and fracture risk in osteoporosis patients [29]. Nevertheless, MRONJ remains a condition that can severely affect quality of life. It is therefore essential to communicate individual MRONJ risk to patients and caregivers clearly, to ensure long-term adherence to medical and oral health programs. Given the continual introduction of new and potentially high-risk medications, healthcare professionals must keep the literature up to date and integrate new data into clinical decision-making [26].

CONCLUSIONS AND RECOMMENDATIONS

The management of periodontal diseases in patients with rheumatologic disorders requires a multidisciplinary approach, focusing on both control of systemic inflammation and prevention of drug-related complications. In autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and vasculitis, regular periodontal screening should be integrated into routine care. Gingival health should be monitored as a potential indicator of disease activity. Simple, low-cost, and repeatable interventions—such as plaque control and scaling and root planing (SRP)—

Table 5. Recommended Discontinuation and Resumption Timing of Antiresorptive and Anti-angiogenic Drugs [26]

Patient Group	Drug	Discontinuation Timing	Resumption Timing
High-Dose AR (R_+ and R_{++})	Bisphosphonates	1 week before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Denosumab (Xgeva®)	3 weeks before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Bevacizumab	5–8 weeks before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Sunitinib	1 week before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Everolimus	1 week before surgery	After wound healing (4–6 weeks post-op)
Low-Dose AR (R_+)	Bisphosphonates	1 week before surgery	After wound healing (4–6 weeks post-op)
Low-Dose AR (R_+)	Denosumab (Prolia®)	No drug holiday required	—

can significantly reduce systemic inflammation and potentially decrease glucocorticoid requirements.

In vasculitic conditions like granulomatosis with polyangiitis (GPA), characteristic findings such as "strawberry gingivitis" or ulcerative oral lesions should be carefully evaluated, as they may serve as early diagnostic clues or markers of disease relapse.

For patients at risk of MRONJ, surgical decision-making must consider antiresorptive drug dosage and regimen. In cases of high-dose (oncologic) therapy, procedures such as implant placement or bone augmentation should be avoided. In contrast, for low-dose osteoporosis regimens, surgical procedures may be safely performed under atraumatic techniques, with primary closure and antiseptic support protocols. The implementation of drug holidays should be individualized, considering patient-specific risk factors and pharmacokinetic properties of the medications—particularly denosumab, where timing is critical.

Looking ahead, more randomized controlled trials are needed to evaluate the impact of periodontal therapy on rheumatologic disease activity and bone mineral density. Longitudinal studies investigating the correlation between periodontitis-related biomarkers (such as aMMP-8, citrullinated proteins, and *P. gingivalis* load) and systemic inflammation would provide valuable diagnostic and prognostic insights. Moreover, clinical trials comparing the effects of traditional versus biologic DMARDs on alveolar bone metabolism could guide the development of personalized treatment strategies.

Finally, the implementation of personalized preventive and therapeutic protocols, combined with prospective evaluation of emerging pharmacologic agents, is essential. A strong communication bridge between rheumatology and dentistry, supported by patient education, will not only reduce oral complications but also improve the overall management and quality of life of patients with rheumatologic diseases.

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