Joint and oral health: The overlooked connection between rheumatoid arthritis and periodontitis (Review)

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Abstract. Rheumatoid arthritis (RA) and periodontitis are chronic, progressive inflammatory disorders that exhibit a notable bidirectional association, increasingly recognized in both rheumatology and periodontology. Epidemiological research has revealed a higher prevalence and severity of periodontitis in individuals with RA, indicating an association that may reflect shared immunological mechanisms. Both conditions are characterized by immune dysregulation, involving the overproduction of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-17, which mediate tissue destruction in joints and periodontal tissues alike. A significant microbiological connection has been identified in periodontal pathogens, particularly *Porphyromonas gingivalis*, which produces peptidyl arginine deiminase and induces protein citrullination. Notably, other microbes, such as *Aggregatibacter actinomycetemcomitans*, which can induce neutrophil hypercitrullination, have also been implicated in this association. These microbial mechanisms are considered to contribute to the formation of anti-citrullinated protein antibodies, although causality has not been definitively established. Immunologically, the overlapping inflammatory cascades and shared genetic predispositions underscore the systemic link between the two diseases. Therapeutically, anti-rheumatic treatments, particularly biologics targeting TNF-α and IL-6, may provide benefits in periodontal health; however, the currently available evidence remains inconsistent and not universally accepted. This inter-association emphasizes the need for integrated medical-dental approaches, promoting early diagnosis and collaborative management to improve overall patient outcomes and quality of life. The present review synthesizes evidence published since 2020, prioritizes testable salivary and microbial biomarker candidates (e.g., citrullinated vimentin, citrullinated α-enolase/CEP-1, neutrophil proteases and oral microbiome signatures), and translates these findings into practical screening and co-management steps for rheumatologists and periodontists.

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Contents

1. Introduction
2. Historical background
3. Epidemiological data
4. Pathophysiology
5. Common pathogenetic mechanisms
6. Correlative studies and animal models
7. Pathogenic theories
8. Clinical manifestations
9. Diagnostic considerations
10. Screening for overlap and prognosis
11. Management and treatment
12. Conclusions and future directions

1. Introduction

Rheumatoid arthritis (RA) and periodontitis are two prevalent chronic inflammatory conditions with profound systemic and local consequences. RA, a systemic autoimmune disease, predominantly affects synovial joints, leading to progressive joint destruction and systemic comorbidities, including cardiovascular disease and osteoporosis. Periodontitis, on the other hand, is a destructive inflammatory disease of periodontal tissues characterized by bone loss and potential tooth loss if left untreated (1). While they affect different anatomical regions, pathophysiological mechanisms underlying both diseases show considerable overlap, particularly in the context of immune-mediated inflammation.

Recent systematic reviews and large population cohorts confirm a bidirectional association between periodontitis and RA, with periodontitis linked to a higher risk of developing RA and patients with RA exhibiting a greater periodontal burden (2-4). However, current evidence still supports an

association rather than a definitive causal association (5). The present review summarizes the interconnectedness of oral health conditions, examining inflammatory mechanisms, the role of oral pathogens and clinical implications for the management of these conditions.

2. Historical background

RA and periodontitis, although distinct in their anatomical manifestations, share a rich and evolving medical history marked by significant advancements in understanding their pathogenesis and clinical management. RA has been a subject of medical interest since the 19th century, with Alfred B. Garrod formally distinguishing it from other forms of arthritis in 1859 (6). Early conceptions of RA were grounded in the notion of chronic synovial inflammation; however, the discovery of rheumatoid factor (RF) in the early 20th century and the subsequent identification of autoantibodies, such as the anti-perinuclear factor in the 1960s, later recognized as a precursor to the modern anti-citrullinated protein antibody (ACPA) tests, marked a pivotal shift toward recognizing RA as an autoimmune condition. These immunologic insights lay the groundwork for the development of biological and targeted therapies, most notably tumor necrosis factor-α (TNF-α) inhibitors, which markedly alter disease outcomes by reducing inflammation, attenuating joint destruction and improving the quality of life of patients. Despite these advancements, RA continues to be a progressive systemic disorder with multifaceted manifestations beyond joint involvement (7).

In parallel, periodontitis has been recognized as a significant oral health concern for the millennia, with archeological evidence of periodontal destruction found in ancient human remains. However, it was not until the 20th century that its microbial etiology was firmly established. The identification of specific periodontal pathogens, such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*, revolutionized the understanding of periodontitis as a biofilm-mediated disease (8). This paradigm shift was further reinforced in the 1970s with the emergence of the microbial biofilm concept, which emphasized the structured and cooperative nature of bacterial communities in dental plaque. In addition to microbial research, increasing attention has been paid to the host immune response, particularly the role of inflammatory cytokines in mediating periodontal tissue breakdown (9). Together, these discoveries have shaped the modern view of periodontitis as a chronic inflammatory disease driven by complex interactions between dysbiotic microbial communities and a dysregulated host immune response.

The historical development of knowledge surrounding RA and periodontitis highlights a shared trajectory wherein advances in immunology and microbiology have informed both diagnostic and therapeutic approaches. This convergence has sparked growing interest in their potential bidirectional association, particularly in the context of systemic inflammation and immune modulation (10).

3. Epidemiological data

RA and periodontitis share common epidemiological features in that both conditions are prevalent worldwide and exhibit sex-based differences. RA affects ~0.5-1% of the global population, with women being more frequently affected than men. Onset typically occurs between the ages of 30 and 50 years. Global epidemiological studies suggest that periodontitis affects >50% of adults, with estimates ranging from 45-55% for any form of disease. Notably, ~10-15% of adults are affected by severe periodontitis, while the remainder exhibit mild-to-moderate disease. The prevalence varies substantially depending on population, socioeconomic status, and risk factors (11).

Numerous studies have highlighted the connection between RA and periodontitis, with several population-based studies revealing a greater prevalence of periodontitis in patients with RA than in healthy controls (12). The meta-analysis by de Pablo *et al* demonstrated that patients with RA are at a 2-fold greater risk of developing moderate-to-severe periodontitis. Additionally, patients with periodontitis show a greater prevalence of RA, particularly when the levels of serological markers, such as anti-cyclic citrullinated peptide antibodies are elevated. Current evidence supports an association, but does not confirm causality (13).

One particularly notable finding was derived from the study of *Porphyromonas gingivalis*, a key periodontal pathogen. This bacterium is capable of generating citrullinated peptides, which are major targets of autoantibodies in RA, suggesting a microbial trigger for the autoimmune response observed in RA (14).

4. Pathophysiology

RA and periodontitis are both chronic inflammatory diseases characterized by dysregulated immune responses and progressive tissue destruction, albeit occurring in different anatomical sites. RA primarily affects the synovial joints and is classified as an autoimmune disease. It arises from a complex interplay of genetic predispositions, environmental exposures and immune dysregulation (15). A key genetic factor linked to RA susceptibility is the presence of specific HLA-DRB1 alleles, particularly those encoding the 'shared epitope', a conserved amino acid sequence associated with an increased risk. Environmental triggers, such as cigarette smoking and exposure to certain microbes, can initiate an aberrant immune response in genetically susceptible individuals, leading to chronic synovial inflammation (2,15).

Immunologically, RA is characterized by the infiltration of immune cells, including $CD4^+$ T-cells, B-cells, macrophages and neutrophils into the synovial membrane. These cells release pro-inflammatory cytokines, such as TNF-α, interleukin (IL)-1β, IL-6 and IL-17, which sustain the inflammatory environment and contribute to synovial hyperplasia and pannus formation (16). The receptor activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) axis is critically involved in bone remodeling in RA; an imbalance favoring RANKL promotes osteoclastogenesis and bone resorption, leading to characteristic joint destruction (15).

Similarly, periodontitis is driven by a chronic immune-inflammatory response initiated by the accumulation of pathogenic subgingival bacteria, such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*. These organisms form structured

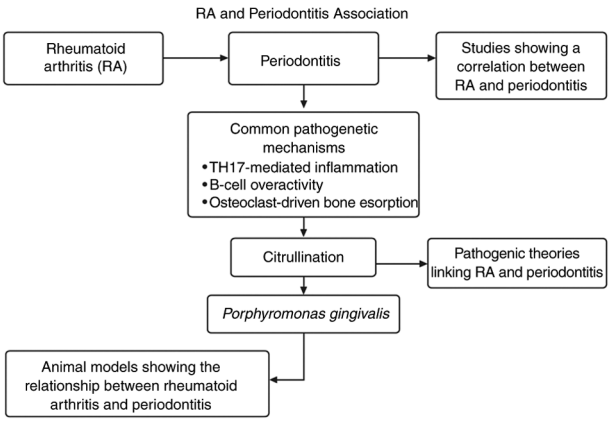

Figure 1. Common pathogenic mechanisms. Shared pathogenic mechanisms linking RA and periodontitis. Periodontal infection and dysbiosis (notably *Porphyromonas gingivalis* and other periodontopathogens) promote protein citrullination, neutrophil hyperactivation and release of proteases and systemic cytokine elevation (TNF-α, IL-6 and IL-17). These processes can amplify anti-citrullinated protein antibody formation, receptor activator of nuclear factor-kappa B ligand-driven osteoclastogenesis and systemic inflammation that contribute to synovial damage in RA and alveolar bone loss in periodontitis. RA, rheumatoid arthritis.

biofilms on tooth surfaces and subvert the host immune response, leading to a persistent inflammatory state. Immune cell infiltration in gingival tissues involves neutrophils, macrophages, dendritic cells, and T helper 17 (Th17) cells, with IL-17 playing a pivotal role in sustaining inflammation. IL-17 enhances neutrophil chemotaxis and stimulates the release of matrix metalloproteinases (MMPs), which degrade extracellular matrix components and contribute to connective tissue breakdown (17).

Moreover, the RANKL/OPG axis is also dysregulated in periodontitis. The increased expression of RANKL by activated T-cells and osteoblasts enhances osteoclast differentiation and activity, resulting in alveolar bone resorption and periodontal attachment loss. The overlapping pathogenic mechanisms, particularly the roles of proinflammatory cytokines, Th17 cells and the RANKL/OPG pathway, highlight the shared molecular pathways between RA and periodontitis, supporting the growing body of evidence linking these two chronic inflammatory diseases (18).

5. Common pathogenetic mechanisms

The overlapping immunopathological mechanisms between RA and periodontitis suggest a bidirectional association (Fig. 1). Both diseases are characterized by excessive inflammation mediated by Th17 cells and increased levels of IL-17. This cytokine promotes the activation of osteoclasts via the RANKL/OPG axis, leading to bone resorption in both the joints in RA and the alveolar bone in periodontitis (19).

Another key intersection is the presence of citrullinated proteins. Among periodontal pathogens, *Porphyromonas gingivalis* produces peptidyl arginine deiminase, which catalyzes the citrullination of host proteins, thereby providing a possible link to ACPA formation. In addition, *Aggregatibacter actinomycetemcomitans* can induce neutrophil hypercitrullination, representing another microbial mechanism potentially associated with RA. These findings highlight that multiple periodontal pathogens may contribute to autoimmune responses, although a definitive causal role has not yet been established. These citrullinated peptides can initiate an autoimmune response in genetically susceptible individuals, contributing to the development of RA (16,20).

Systemic inflammation is another common feature of both diseases, with elevated levels of pro-inflammatory cytokines, such as TNF-α, IL-6 and C-reactive protein (CRP). These markers not only reflect disease activity, but may also contribute to the pathogenesis of both RA and periodontitis (1).

6. Correlative studies and animal models

Several observational studies have confirmed the association between RA and periodontitis. The Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study, for example, revealed that individuals with severe periodontitis are at an increased risk of developing RA (21). Other studies have shown that patients with RA with periodontitis exhibit increased levels of systemic inflammation and worse disease outcomes (5,7).

Clinical intervention studies have also demonstrated the benefits of periodontal therapy in the management of RA. For example, Kaushal *et al* (22) reported that non-surgical periodontal treatment improved the disease activity score in 28 joints (DAS-28) in patients with RA, suggesting that managing periodontal health can have a positive impact on systemic inflammation in patients with RA.

Animal models have also been instrumental in elucidating the bidirectional association between RA and periodontitis. In a previous study, in a mouse model of collagen-induced arthritis, it was shown that when combined with *Porphyromonas gingivalis* infection, animals developed more severe joint damage (23). Similarly, the ligature-induced periodontitis model in rats has been used to determine how periodontal disease exacerbates systemic inflammation and joint pathology (24).

Double-hit models, in which both RA and periodontitis are induced simultaneously, provide further evidence for the synergistic association between these two diseases. These models reveal elevated levels of IL-17, RANKL and MMPs, mimicking the clinical scenario observed in human patients (25,26).

7. Pathogenic theories

There are two primary theories that explain the connection between RA and periodontitis, as follows:

i) Autoimmune hypothesis. Periodontal inflammation leads to the systemic dissemination of citrullinated peptides, which prime the immune system to produce ACPAs. These autoantibodies target citrullinated proteins, leading to the development of RA (27).

ii) Microbial hypothesis. Periodontal pathogens, including *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, may translocate to joints or initiate immune responses that cross-react with joint tissues. DNA from oral

bacteria has been detected in synovial fluid, supporting their potential association with the pathogenesis of RA, although direct causality remains unproven (28).

8. Clinical manifestations

The clinical manifestations of RA and periodontitis involve inflammation and progressive tissue destruction, with overlapping inflammatory pathways that complicate diagnosis and management when both conditions are present.

RA typically presents with symmetrical polyarthritis, affecting both large and small joints, often beginning in the hands and feet. Symptoms include joint pain, stiffness, swelling and warmth of the affected joints (15,20). Morning stiffness that persists for at least 1 h tends to improve with movement. Over time, joint damage may cause deformities, such as ulnar deviation and swan-neck deformities. Systemic symptoms include fatigue, low-grade fever, weight loss and anemia. Extra-articular manifestations, such as rheumatoid nodules, cardiovascular complications, such as atherosclerosis, pulmonary fibrosis and severe rheumatoid vasculitis can also occur, affecting small blood vessels and causing skin lesions and ulcers (1,29).

Periodontitis, an inflammatory disease affecting the supporting structures of the teeth, is characterized by gingival inflammation, pocket formation, alveolar bone loss and tooth mobility. Clinical signs include bleeding gums, swelling and redness, which worsen with brushing or probing. As the disease progresses, deep periodontal pockets form, leading to tooth mobility and visible bone loss on radiographs. Gingival recession exposes tooth roots, causing sensitivity and aesthetic concerns. Severe periodontitis may result in abscesses, swelling, pain and pus formation. Halitosis often accompanies the disease due to bacterial activity in the pockets (30,31).

The bidirectional association between RA and periodontitis complicates clinical management. Patients with RA are often more susceptible to developing periodontal disease due to factors, such as immunosuppressive therapy, reduced manual dexterity and medication side-effects such as xerostomia. In turn, periodontitis in patients with RA can exacerbate systemic inflammation, worsen joint symptoms, and create a vicious cycle that accelerates joint damage and decreases treatment effectiveness. Chronic periodontal inflammation can significantly affect RA disease activity, rendering both conditions more difficult to manage (32).

9. Diagnostic considerations

The diagnosis of both RA and periodontitis involves a combination of clinical evaluation, laboratory testing and imaging studies. For patients with overlapping RA and periodontitis, early and accurate diagnosis is crucial for implementing effective treatment strategies.

Diagnosis of RA. The diagnosis of RA begins with a thorough clinical history and examination. Symmetrical joint involvement and morning stiffness lasting for >1 h are key symptoms of RA. Specific serological markers, including RF, which is positive in 60-80% of patients with RA, and ACPAs, which have high specificity for RA, help confirm the diagnosis. Additionally, elevated erythrocyte sedimentation rates and CRP levels are indicative of systemic inflammation and provide evidence of active disease (1).

Imaging analyses play a crucial role in assessing joint damage. Radiographs reveal joint space narrowing, erosions and periarticular osteopenia, which are characteristic of RA. Ultrasound and MRI are valuable tools for detecting early inflammatory changes and assessing synovial thickening and fluid accumulation, often before radiographic damage is evident (33,34).

Diagnosis of periodontitis. The diagnosis of periodontitis is based on clinical and radiographic criteria. A clinical evaluation includes measuring the probing depth and clinical attachment level, which assess the extent of pocket formation and tissue destruction. Indicators, such as bleeding on probing and tooth mobility are suggestive of active disease. Radiographs provide essential information regarding the extent of alveolar bone loss and the severity of periodontal involvement (30).

Periodontitis is classified on the basis of its severity and extent, ranging from mild gingivitis to severe periodontitis, which is characterized by significant bone loss and deep periodontal pockets (5). This classification is vital for determining the appropriate treatment approach.

10. Screening for overlap and prognosis

Given the potential for increased disease severity when both RA and periodontitis co-occur, screening for periodontal disease in patients with RA and vice versa is strongly recommended. Routine oral assessments for patients with RA can aid in the early detection and management of periodontal disease, which may, in turn, aid in controlling the disease activity of RA. Conversely, screening patients with RA for periodontal involvement can improve the management of both conditions through a coordinated care approach (29,31).

Prognosis. The prognosis of patients with RA and periodontitis is complex due to the interaction between systemic inflammation and oral health. Both diseases contribute to the other's progression, with periodontal inflammation exacerbating RA symptoms and vice versa. In patients with RA, periodontitis increases systemic inflammation, leading to elevated CRP and pro-inflammatory cytokine levels, which may exacerbate joint symptoms. Some research suggests that this could reduce responsiveness to disease-modifying anti-rheumatic drugs and biologics, although evidence remains limited and further studies are required to confirm this association (11). Evidence suggests that periodontal treatment can improve RA symptoms by reducing systemic inflammation and potentially slowing joint destruction (12). In patients with periodontitis, RA can contribute to the rapid progression of periodontal disease, and immunosuppressive therapies can impair the ability of the body to manage periodontal pathogens, leading to more severe disease. Integrated care for improved prognosis is crucial, and collaboration between rheumatologists and periodontists can help manage both conditions more effectively (6,35).

11. Management and treatment

The management of RA and periodontitis requires a comprehensive, interdisciplinary approach that addresses both local and systemic factors. Treatment for both conditions aims to

Table I. Management of rheumatoid arthritis.

Treatment Modality	Description	Considerations in periodontal context
NSAIDs	Alleviate pain and control inflammation; provide symptomatic relief.	Useful for managing inflammation but do not alter disease progression.
DMARDs (e.g., methotrexate)	Slow disease progression and prevent joint destruction.	May improve systemic inflammation; immune modulation can affect periodontal healing.
Biological agents (e.g., TNF inhibitors)	Target proinflammatory cytokines for severe RA treatment.	Enhanced control of inflammation may benefit periodontal outcomes.
Corticosteroids	Used during flare-ups to control inflammation; long-term use limited due to side-effects.	Long-term use may cause osteoporosis, complicating periodontal therapy and bone health.
Nonpharmacological interventions	Physical therapy, exercise, occupational therapy to maintain joint function and. mobility	Improved physical health and reduced disability can enhance oral hygiene practices.
Surgical interventions	Repair or replacement of severely damaged joints.	Restoration of function may indirectly improve oral hygiene ability and overall health.

RA, rheumatoid arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs.

control inflammation, prevent further damage and improve the overall quality of life of affected individuals.

Management of RA. The primary goal of RA treatment is to control joint inflammation and prevent further damage (Table I) (36,37).

Management of periodontitis. The management of periodontitis primarily focuses on eliminating the source of infection, reducing inflammation and regenerating lost tissue (Table II) (38-40).

Although some clinical research has reported improvements in periodontal parameters with anti-TNF-α and anti-IL-6 therapy, findings are not consistent across populations (7). Thus, any potential periodontal benefit of RA biologics should be interpreted with caution, as current evidence does not establish a definitive therapeutic effect.

Impact of periodontal treatment on RA. Effective periodontal treatment has been shown to have a significant positive effect on RA by reducing systemic inflammation, a key contributor to disease pathogenesis. It has been demonstrated that periodontal therapy can lead to lower levels of CRP, a marker of systemic infection, and improve the DAS-28, reflecting better control over RA symptoms (41). The bidirectional association between RA and periodontitis suggests that managing one condition can help improve the outcomes of the other, reinforcing the need for a holistic and interdisciplinary approach to patient care (20,42). Recent randomized trials and systematic reviews have reported that non-surgical periodontal therapy (scaling and root planning ± local/systemic adjuncts) can reduce systemic inflammatory markers and modestly reduce RA disease activity (mean DAS-28 reductions reported in meta-analyses ~0.3-0.5 points), although the results are heterogeneous and patient-selection dependent. These data support routine periodontal screening in RA clinics and collaborative management pathways where periodontitis is present (43). These findings underscore the importance of an integrated approach to treatment, where addressing periodontal disease can directly enhance the management of RA.

12. Conclusions and future directions

Research gaps and future directions. Despite progress being made in the understanding of the association between RA and periodontitis, there gaps remain in research. Longitudinal studies are required to determine whether treating one disease can prevent the onset or progression of the other, with a focus on biomarkers of disease progression and the effect of periodontal treatment on RA progression. Specific biomarker candidates include: Citrullinated vimentin (anti-MCV), implicated in osteoclast activation and bone resorption; citrullinated α-enolase/CEP-1 and related ACPA specificities that cross-react with bacterial enolases; neutrophil-derived proteases (e.g., elastase, proteinase-3) detectable in saliva and gingival crevicular fluid reflecting neutrophil hyperactivation; and oral microbiome signatures (16S/shotgun panels) that may distinguish early RA or predict periodontal disease progression. Evidence of the role of citrullinated vimentin in bone resorption has been demonstrated in animal models, and clinical studies have revealed increased levels of antibodies against citrullinated bacterial epitopes in early-stage RA (32,44,45). Incorporating these markers into prospective, standardized cohort studies will clarify temporal relations and may enable

Table II. Management of periodontitis.

Treatment Modality	Description	Purpose/impact
Scaling and root planing (SRP)	Mechanical removal of plaque and calculus from root surfaces; smoothing of roots.	Reduces bacterial load, promotes healing, and establishes a healthier oral environment.
Antibiotic therapy	Use of topical or systemic antibiotics targeting specific pathogens (e.g., *Porphyromonas gingivalis*).	Enhances bacterial control, particularly in aggressive or refractory cases.
Surgical therapy	Procedures to regenerate lost periodontal tissue or reduce deep pockets (e.g., flap surgery, bone grafts).	Improves access for debridement, restores periodontal architecture, and reduces pocket depth.
Host modulation therapy	Use of agents such as low-dose doxycycline to modify the inflammatory response of the host.	Reduces tissue destruction, preserves periodontal support, and enhances treatment outcomes.

precision screening in high-risk patients. Potential candidates under current investigation include citrullinated vimentin and α-enolase as autoantigens, salivary protease markers reflective of periodontal tissue destruction, and microbiome signatures specific to periodontitis. Incorporating these markers into longitudinal studies may clarify the temporal association between RA and periodontitis and guide precision medicine approaches. Understanding the role of specific microbes and their interactions with the host immune system could provide new insights into the pathogenesis of both diseases and the genetic basis for the overlap in susceptibility to RA and periodontitis. Future clinical trials are required to evaluate the efficacy of co-management strategies for RA and periodontitis, assessing whether integrated care improves patient outcomes in both oral and systemic health.

Limitations of current evidence. While numerous studies support an association between RA and periodontitis, the current body of evidence has several limitations. A number of investigations are cross-sectional in nature, rendering it difficult to establish temporal associations or causality. Potential confounding factors, such as smoking, socioeconomic status, diabetes and other systemic comorbidities may influence both diseases, and complicate the interpretation of the associations. Furthermore, heterogeneity in diagnostic criteria for both RA and periodontitis across studies reduces comparability. Sample sizes in interventional trials are often small, limiting generalizability. Longitudinal and multicenter studies with standardized definitions are thus warranted to strengthen the evidence base.

In conclusion, the association between RA and periodontitis is complex, with inflammation being a common factor accelerating their progression. This highlights the need for integrated care approaches that address both systemic and oral health. Early diagnosis and effective management of periodontitis in patients with RA can improve patient outcomes, reduce joint damage and enhance treatment response. Collaborative efforts between rheumatologists and periodontists are essential to unravel the underlying mechanisms linking these diseases. Future research into biomarkers, genetic predispositions and microbial interactions will lead to personalized therapies and to an improved quality of life for affected patients. Bridging the gap between oral and systemic health care is now necessary for holistic, patient-centered treatment.

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Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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