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THE INTERRELATIONSHIP BETWEEN THE ORAL MICROBIOME AND RHEUMATOID ARTHRITIS: EXPLORING MUTUAL INFLUENCES AND CLINICAL IMPLICATIONS

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ABSTRACT

Introduction and objective: Periodontitis (PD) is caused by dysbiosis of the oral microbiome (OMB). The prevalence of PD is increased in RA patients. Both conditions have the ability to activate common inflammatory pathways. The OMB shift contributes to more severe course of PD and RA. This paper aims to summarize the impact of OMB on chronic inflammation in the pathogenesis of PD and RA.
Description of the state of knowledge: The OMB can influence chronic inflammation and protein citrullination. The presence of antibodies against citrullinated peptides (ACPA) correlates with an increased incidence and severity of periodontitis. While numerous studies have reported a relationship between the OMB, PD and RA, the role of specific bacteria in RA remains unclear.
Methodology: A literature review was conducted using two databases - PubMed and Google Scholar - with search terms such as "oral microbiome", "rheumatoid arthritis", "periodontal health", "oral microbiota", "periodontal disease". Articles published within the last eight years were prioritized.
Conclusions: PD is more prevalent and severe particularly in ACPA-positive RA patients. Alterations in OMB are associated with systemic inflammation, contributing to RA progression. and worsening periodontal conditions. Periodontal treatment shows a potential to reduce RA activity, emphasizing the importance of dental care in RA. Anti-inflammatory treatments may restore oral homeostasis. Targeting the OMB offers a potential for managing RA and PD. Further research is needed to establish guidelines for personalized therapies and prophylaxis.

KEYWORDS

Oral Microbiome, Rheumatoid Arthritis, Periodontal Disease, Periodontal Health, Oral Microbiota

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Introduction

The oral microbiome (OMB) comprises a complex and diverse community of microorganisms inhabiting the oral cavity. Periodontal health relies on the maintaining host–microbe homeostasis in the periodontium. Disruption of this equilibrium—due to microbial imbalances or host immunoregulatory defects—triggers a pathologic cycle leading to periodontal disease [1]. Two primary forms of periodontal disease are recognized: gingivitis and periodontitis (PD). PD is a chronic dysbiotic inflammatory condition associated with altered plaque biofilms and characterized by the progressive destruction of the tooth-supporting structures. It manifests as alveolar bone loss, periodontal pocketing, gingival bleeding, and, if untreated, may result in tooth loss [2, 3].

Rheumatoid arthritis (RA) is a prevalent chronic inflammatory disease leading to cartilage and bone damage, often accompanied by extra-articular manifestations, such as rheumatoid nodules, pulmonary involvement, vasculitis, and systemic comorbidities like atherosclerosis, which elevate cardiovascular risk [4]. RA affects 0.5–1% of adults, predominantly women aged 50–60. Its etiology remains unclear, but involves genetic predispositions and environmental factors that contribute to a pre-RA state, marked by the presence of antibodies against citrullinated peptides (ACPA) and/or rheumatoid factor (RF), immune tolerance disruption, and abnormal cytokine signaling [5]. ACPA and RF are believed to promote inflammation through complement activation and immune complex formation, making ACPA a marker of worse disease progression [5, 6, 7]. Environmental factors such as smoking, bacterial periodontitis, coffee consumption, and exposure to silica dust have been identified as risk factors for RA, influencing protein citrullination [5].

A higher prevalence of periodontitis in individuals with RA compared to controls was suggested. The presence of ACPA and RF correlates with an increased incidence and severity of periodontitis, indicating a more aggressive disease course in ACPA-positive patients [8]. This association has prompted investigations

into the role of oral microbiota, particularly *Porphyromonas gingivalis*, in RA pathogenesis. This bacterium exhibits proteinase and collagenase activities, promoting autoantigen formation and immune dysregulation, thereby linking periodontal infections to RA [9]. Studies have shown distinct subgingival microbial profiles in RA patients with moderate to severe periodontitis compared to those with no or mild disease. Species such as *Desulfobulbus sp.*, *Prevotella sp.*, and *Tannerella sp.* are abundant in severe cases, whereas *Prevotella sp.* and *Porphyromonas sp.* dominate in mild cases [8]. Notably, no significant difference in the prevalence of *P. gingivalis* was observed across severity levels [7].

This paper aims to summarize the relationship between periodontal health and rheumatoid arthritis, reviewing the impact of oral microbiota on the prevalence and severity of RA symptoms.

Methodology

For the purpose of this article a literature review was conducted using two databases - PubMed and Google Scholar - with search terms such as "oral microbiome", "rheumatoid arthritis", "periodontal health", "oral microbiota", "periodontal disease". Articles published within the last eight years were prioritized.

1. Rheumatoid arthritis and periodontitis

The connection between RA and PD has been supported by numerous studies [8–11]. Although they have different etiology - autoimmune versus infectious, both diseases share genetic similarities, risk factors, the capability to activate homogeneous inflammatory pathways and the process of bone destruction [12]. Regarding genetics, both RA and PD show high frequencies of HLA-DR4 tissue antigens [9]. Mutual risk factors, such as smoking, may also enhance protein citrullination, which plays an important role in the pathogenesis of both diseases [1, 2, 5]. Several studies have reported an increased prevalence of periodontitis in RA patients compared to controls [10, 12, 13]. Based on similarities between the two diseases, a "two-hit" model was proposed, suggesting that the oral microbiome (first "hit"), through interaction with bone-destructive diseases (second "hit") in another location in the body (e.g. joint capsule), may co-induce periodontitis [14]. Studies in rodents have shown that chronic systemic inflammation in RA can determine the susceptibility to periodontitis in RA patients [12, 15]. This case-control study [10], found a significantly higher prevalence of PD in RA patients (71.5%) compared to osteoarthritis (OA) controls (51.6%). However, no significant difference in periodontal disease severity was observed between RA and OA group. While RA activity, measured by DAS28-ESR, showed no correlation with periodontitis severity, disease duration and activity correlated with tooth loss [10]. These results are consistent with a similar tendency reported by Disale et al. [16], where a 45% prevalence of PD in RA patients versus 33% in OA patients was reported. Interestingly, Miculus et al. [11] reported that PD in RA patients is associated with higher swollen joint counts, higher DAS28-CRP scores, and greater radiographic joint damage. Consistently, this study found that the comorbidity of RA and PD was associated with higher RA activity indicators - including DAS28-CRP, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and joint count - compared to the RA without PD group, regardless of the treatment applied. Moreover, patients with higher RA activity (DAS28-CRP) exhibited worse periodontal conditions, compared to those with low RA activity [17]. Interestingly, Eriksson et al. [8] established no link between periodontitis severity and RA disease activity - measured as DAS28, health assessment (HAQ-score) and CRP levels, while suggesting that ACPA-positivity correlates with moderate to severe periodontitis. Existing research confirms that ACPA-positive RA patients experience more severe periodontitis than their ACPA-negative counterparts, regardless of anti-inflammatory medication use or the presence of subgingival *P. gingivalis* [8, 10, 11]. A similar outcome was observed among U.S. veterans with RA regarding RF-positivity, in whom RF titers were positively associated with periodontitis severity [11, 16, 18]. Furthermore, RF-positive RA patients exhibited greater probing pocket depths and gingival recession compared to seronegative RA patients [10]. These observations suggest an increased susceptibility to periodontal diseases in seropositive patients.

The impact of RA activity on the severity of periodontitis remains ambiguous. However, evidence indicates that periodontitis may act as a trigger, exacerbating RA symptoms. This hypothesis could be supported by findings from Sher et al., who reported a high prevalence of advanced PD in patients with new-onset RA, despite their young age and limited smoking history [19]. The presence of PD at the time of new-onset RA diagnosis suggests that it is more likely a trigger of systemic inflammation, than a consequence of RA [20].

2. Autoantibodies and protein citrullination in RA and PD

2.1 RA Pathogenesis and protein citrullination

Antibodies against citrullinated peptides (ACPA) and rheumatoid factor (RF) are the predominant autoantibodies detected in the serum of patients with RA. RF are characterized by higher diagnostic sensitivity, however lower specificity compared to ACPA [21]. Based on current knowledge, ACPA can be detected at high titers during the pre-RA stage—that is, in individuals at high risk of developing RA but who do not yet meet the diagnostic criteria. Therefore, ACPA are considered early markers of the disease and predictors of a more severe course and rapid progression. ACPA target proteins such as: filaggrin, fibrinogen, vimentin, α-enolase, inducing the citrullination, which is a post-translational modification of arginine residues, catalyzed by peptidylarginine deiminase (PAD) enzymes. The binding of ACPA to citrullinated proteins can activate the complement system, leading to the release of pro-inflammatory cytokines including tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). This inflammatory cascade stimulates osteoclasts and fibroblast-like synoviocytes (FLS), promoting joint inflammation and damage [6, 7]. Additionally, ACPA interaction with osteoclasts induces the secretion of interleukin-8 (IL-8), contributing to bone erosion and associated pain. Collectively, these pro-inflammatory processes in the synovium and synovial fluid accelerate the progression of RA [22]. It has been observed that both RA and periodontitis have a potential to alter a local and systemic cytokine profile. One study [23] aimed to explore the association of levels of interleukin -6, -10, -17, and -23 with RA symptoms, applied treatment and coexisting PD. The results indicated that elevated IL-10 levels were associated with prolonged morning stiffness and reduced serological markers (ACPA, RA). Conversely, higher IL-17 levels were interpreted as indicative of increased RA activity, no significant association between IL-17 titers and dental health was confirmed. Elevated IL-23 levels were observed in patients with higher RF titers and greater periodontal disease severity. Furthermore, the study demonstrated leflunomide's potential to modulate Il-23 pathways, thereby reducing periodontal burden. Notably, no significant differences were found in serum IL-6 levels. Additionally, Eriksson et al. [8] identified elevated serum and salivary levels of APRIL, a TNF-receptor family member involved in B-cell maturation, in RA patients with moderate or severe PD. While these findings highlight some associations, the authors underscore the need for further research, particularly concerning the complex interplay between disease activity and medication effects on periodontal burden [23]. It is noteworthy to mention that ACPA positivity is influenced not only by joint disease and genetic factors, but also by independent risk factors such as older age, female sex, and smoking [24-26]. Interestingly, a review involving over 40,000 participants did not confirm a definitive link between periodontitis and increased ACPA positivity. However, this conclusion was based on self-reported questionnaires, which are less reliable than studies involving oral examinations conducted by experienced clinicians. [24].

2.2 Role of *P. gingivalis* in protein citrullination

It has been suggested that *P. gingivalis* - the key bacteria involved in the pathogenesis of PD - may induce citrullination of both its own and host proteins, potentially triggering the development of RA [27-30]. *P. gingivalis* expresses peptidyl-arginine deiminase (PPAD) and gingipains (cysteine-like proteases), leading to hipercitrullination and disrupting the host's immune signaling network. In this process occurs the release of ammonia, increasing the local pH, creating a favorable environment for *P. gingivalis* survival in periodontal pockets. [31].

Both human PADs and citrullinated proteins are present in the oral mucosa and the periodontal epithelium, facilitating physiological citrullination in these tissues. Mucosal inflammation caused by PD can enable oral bacteria like P. gingivalis to translocate to distant sites, including joints. Additionally, *P. gingivalis* α-enolase shares 82% homology with human α-enolase, which could lead to potential cross-reactivity. In periodontitis, increased citrullination of bacterial proteins may compromise immunotolerance to structurally similar host proteins, potentially mimicking synovial antigens and resulting in the production of ACPA in genetically susceptible individuals. This hypothesis could explain the observed correlation between elevated ACPA titers in RA patients and the presence of PD [32, 33]. Beyond PPAD expression, *P. gingivalis* induces high levels of pro-inflammatory cytokines (e.g., IL-1β, IL-6) via peripheral CD4+ T helper cells and degrades transport proteins such as albumin, lactoferrin, exacerbating inflammation and tissue damage, particularly in aggressive forms of periodontitis [9, 34]. Moreover, PPAD-mediated citrullination of histones influences the formation of neutrophil extracellular traps (NETs), structures aimed at trapping pathogens, suggesting a role for *P. gingivalis* in modulating this defense mechanism [31]. In a murine study, chronic oral infection with *P. gingivalis* prior to the onset of arthritis influenced RA progression through Th17-related pathways [35].

Similarly, in another mouse model, pre-existing periodontitis exacerbated arthritis severity and accelerated disease progression [36]. Engström et al. [37] noted increased citrullination and PAD expression (PAD2 and PAD4) in gingival connective tissue of periodontitis patients, independent of *P. gingivalis* or leukotoxin from *A. actinomycetemcomitans*. Sher et al. [19] observed that *P. gingivalis* is linked with PD severity; however, this association is not unique to RA and does not correlate with ACPA titers. Their study found similar *P. gingivalis* exposure rates in RA patients (78.4%) and controls (83.3%). Cheng et al. [38] have reported that in their study, ACPA-positive individuals at risk of developing RA, showed increased abundance of P. gingivalis and dysbiotic subgingival microbiomes compared to healthy controls. Additionally among ACPA-positive at-risk RA group, periodontally healthy individuals exhibited significantly lower microbial richness compared to healthy controls and early RA group.

3. The oral microbiome (OMB)

3.1 Oral microbiome in periodontitis pathogenesis

The homeostasis of the OMB depends on various factors, including oral hygiene, dietary habits, smoking, gingival inflammation, genetic differences, salivary gland dysfunction and systemic conditions such as diabetes, cardiovascular diseases and connective tissue diseases [39]. When periodontal health is preserved, the OMB predominantly consists of Gram-positive aerobic bacteria, which help maintain the microbiome balance [33]. Sher et al. [19] identified that the healthy OMB is dominated by bacterial phyla such as Bacteroidetes, Firmicutes (Bacillota), Actinobacteria, Proteobacteria (Pseudomonadota), Fusobacteria, Spirochaetes and TM7 (Saccharibacteria). A shift to a dominance of Gram-negative anaerobes fosters local inflammation, initially manifesting as reversible gingivitis. If left untreated, gingivitis progresses to chronic periodontitis, characterized by irreversible tissue degradation. Research highlights some bacterial complexes as highly associated with chronic periodontitis, particularly the "red complex" including three species: *P. gingivalis*, *T. forsythia*, *T. denticola*. The "red complex" is positively associated with periodontal pocket depth and bleeding on probing, which are key markers of disease severity strongly linked to PD severity. Other implicated bacteria include *A. actinomycetemcomitans*, *F. alocis* and representatives of the "orange complex" such as *F. nucleatum* and *P. intermedia* [28, 33, 40].

3.2 The correlation between OMB and RA

Periodontal dysbiosis, characterized by increased microbial diversity and elevated level of bacterial species linked to periodontal disease, is frequently observed in patients with RA (*Table 1*). This dysbiosis contributes to more severe periodontitis and a worsened course of RA. Interestingly, even in RA patients without PD, a shift in the oral biofilm toward periodontitis-associated bacteria has been observed [15, 41, 42]. In RA patients, systemic inflammation accelerates the production of cytokines such as IL-17, Il-2, TNF, INF-γ [13]. Rodent studies have shown that elevated cytokines in RA, including TNF-α, IL-1, IL-6, and IL-17, can influence inflammatory cytokine levels in oral tissues. Increased salivary concentrations of IL-17, TNF-α, and IL-33, along with diminished redox potential, create an environment favorable for obligate anaerobic bacteria. This microbial shift promotes periodontitis [12, 15]. Furthermore, it has been hypothesized that oral pathogens may alter the immune response, triggering the production of ACPA and thereby inducing the development and progression of arthritis [41, 43, 44]. Collectively, these findings may explain the mutual correlation between RA and PD - both the increased susceptibility to PD in RA patients and the influence of PD on arthritis activity.

3.3 The OMB diversity in RA patients

P. gingivalis is considered one of the most important bacteria implicated in PD, however its role in RA pathogenesis remains incompletely understood. Several research groups have sought to quantify and correlate levels of antibodies against this bacterium in RA patients. Mikulus et al. [43] observed that antibodies against *P. gingivalis* were more frequent in RA patients than in controls, though less frequent than in patients with PD. Moreover, Anti-*P. gingivalis* titers correlated with ACPA and CRP levels. Hitchon et al. [44] found that antibody levels against *P. gingivalis* lipopolysaccharides (LPS) were higher in RA patients than in their relatives and unrelated healthy controls. Additionally, they found a positive association between ACPA and anti-*P. gingivalis* LPS in both RA patients and their relatives. This suggests that the immune response may occur independently of RA diagnosis. A 2017 meta-analysis confirmed that RA patients exhibited significantly higher antibody responses against *P. gingivalis* compared to healthy controls [45]. Ogrendik et al. [9] reported higher levels of antibodies against *P. gingivalis*, as well as *P. intermedia*, *P. melaninogenica*, and *B. forsythus* in RA patients serum compared to controls, suggesting their potential roles in RA pathogenesis. No correlation

was found regarding anti-*A. actinomycetemcomitans* antibodies. A 2003 study, reported elevated antibody titers against *B. forsythus* in the synovial fluid, while its significantly decreased serum levels in RA patients compared to those with osteoarthritis (OA). Therefore suggesting active antibody production in synovial tissue [46]. On the other hand, the study of gingival crevicular fluid (GCF) identified *A. actinomycetemcomitans* as the only species capable of reproducing the repertoire of citrullinated antigens in RA joints. Its major virulence factor, leukotoxin A (LtxA), induces neutrophil citrullination and dysregulation of PAD enzymes. Anti-*A. actinomycetemcomitans* antibodies correlated with PD severity and RA-associated autoimmunity. Notably, associations between HLA-DRB1 alleles, ACPA, and RF were observed only in RA patients exposed to *A. actinomycetemcomitans,* not *P. gingivalis* [41]. Martisson et al. [47] and Brewer et al. [48] confirmed a positive correlation between the levels of anti-LtxA antibodies in blood and saliva samples and ACPA titers in RA patients as well as in the individuals with arthritis at risk of RA. According to this knowledge, periodontal exposure to *A. actinomycetemcomitans* might drive immune responses that promote ACPA production, potentially leading to RA onset.

Moving forward to research using methodology based on DNA sampling, in 2016 Zhang et al. [49] highlighted the significant decrease of *Haemophilus spp.* in the saliva of RA patients, negatively associated with serum autoantibody levels. Conversely, *L. salivarius* levels were elevated, particularly in patients with very active RA. Among "red complex" bacteria, *T. denticola* exhibited the highest prevalence in patients with both RA and PD compared to either condition alone or healthy controls. Its presence increased the likelihood of ACPA positivity sixfold [17, 50]. Another study [15] highlighted the enrichment of *Prevotella spp.* in the saliva and subgingival microbiota of RA subjects. Moreover, *P. copri* was found to have a notable potential to induce Th17-related cytokines and is associated with Th17-mediated mucosal inflammation [51]. In a Chinese cohort, *A. actinomycetemcomitans* was significantly more prevalent in RA patients with PD than those without PD. Its abundance correlated with higher DAS28 scores, RF and ACPA titers., probing pocket depth and gingival index, but not with plaque index or clinical attachment loss. Therefore highlighting that *A. actinomycetemcomitans* infection could exacerbate both the RA symptoms and periodontitis severity in RA patients [52]. Another study showed a negative association between presence of *Actinomyces spp.,* and positive between the abundance of *F. fastidiosum, P. micra* and *A. geminatus* and increased count of swollen and tender joints [13]. Conversely, a different study [53] established that higher ACPA titers corresponded to lower levels of *Pophyromonas* and *Aggregatibacter*, suggesting that ACPA may control the colonization of these oral bacteria with a protective effect on oral microbiome in RA patients. In new-onset RA patients (NORA), compared to chronic RA patients, a dominance of "red complex" bacteria was observed, accompanied by a decreased abundance of *Corynebacterium* spp. and *Streptococcus* spp. Interestingly *Prevotella spp.* and *Leptotrichia spp.* were present only in NORA, regardless of PD status. [19]. Various studies have confirmed the presence of an altered OMB already in early stages of RA and in at-risk of RA patients, highlighting reduced abundance of *Defluviitaleaceae spp.* and *N. oralis,* as well as enriched levels of *Prevotella spp.* [54], *P. pleuritidis, T. denticola, P. endodontalis* and *F. alocis sp.* [55]. Some genera were also found to correlate positively with ACPA titers. [54]. Individuals at risk of RA exhibit an oral microbiome (OMB) similar to that of early-RA patients, with an increased abundance of *Prevotella spp.* and *Veillonella spp.* in saliva from both groups compared to healthy controls [56]. Interestingly, the observation of OMB in female RA patients compared to controls, confirmed the domination of Prevotellaceae and Leptotrichiaceae and their positive correlation with ACPA positivity and clinical RA activity. Moreover, *Prevotella spp.* positively correlated with the RF levels, while the abundance of *S. infantis* showed moderate negative correlation with RF titers. Furthermore, increased levels of *Treponema spp.* and Absconditabacteriales were associated with low disease activity, while *Porphyromonas spp.* was more abundant in patients with moderate disease activity. High disease activity was correlated with an enrichment of *Staphylococcus*. [42]. In another study the RA activity has been associated with increased prevalence of *Corynebacterium matruchotii*, *Actinomyces, Veillonella and Streptococcus,* compared to RA patients in remission [57]. Interestingly, while comparing RA and osteoarthritis patients, eight oral bacterial biomarkers were identified that distinguish between the two groups. The RA group tended to exhibit the most complex bacterial community, particularly higher levels of *Prevotella* and *Leptotrichia.* In contrast, OA patients demonstrated increased levels of *Neisseria* and *Haemophilus*, while healthy controls showed higher abundances of *Capnocytophaga* and *Veillonella* [58]. These microbial signatures could serve as non-invasive biomarkers, aiding clinicians in distinguishing between RA and OA.

Based on the knowledge acquired so far, there is undoubtedly a relationship between the oral microbiome and rheumatoid arthritis (RA). However, it is important to remember about additional factors influencing the OMB in RA patients, such as poorer oral hygiene, increased biofilm accumulation, and sicca

syndrome. All together they contribute to periodontal inflammation and exacerbate RA symptoms [59]. Subgingival microbiota diversity varies with disease activity, anti-inflammatory drug use, and comorbidities such as diabetes and smoking. Lopez-Olivia et al. [60] analysed the subgingival biofilm in RA patients with good periodontal health, demonstrating distinct differences in the subgingival microbiota compared to healthy individuals. Certain bacterial species were more prevalent in the RA group, underlining the importance of the oral microbiome in RA development and progression. The researchers suggested targeting the OMB as a potential strategy for new RA treatments.

Table 1. The diversity of the OMB in PD, RA, new-onset RA compared to a healthy OMB.

Healthy OMB [19]	**OMB in periodontitis [19, 33, 40]**		**OMB in RA [19, 42, 49, 52, 60]**		**OMB in new-onset RA [19, 54, 55]**	
Dominant (phylum)	**Dominant (species; phylum)**	**Diminished (species; phylum)**	**Dominant (species; phylum)**	**Diminished (species; phylum)**	**Dominant (species; phylum)**	**Diminished (species; phylum)**
Aerobes or facultative anaerobes: Bacteroidota (21%), Actinomycetota (21.8%), Bacillota (10.9%), Pseudomonadota (16.9%). **Obligate anaerobes:** Fusobacteriota (24%), Spirochaetota (2.5%), Saccharibacteria (1.6%).	**Aerobes or facultative anaerobes:** *Aggregatibacter actinomycetemcomitans;* Pseudomonadota. **Obligate anaerobes:** *Porphyromonas gingivalis;* Bacteroidota[a], *Tannerella forsythia;* Bacteroidota, *Treponema denticola;* Spirochaetota, *Filifactor alocis*; Bacilliota, *Fusobacterium nucleatum*; Fusobacteriota, *Prevotella intermedia*; Bacteroidota, Saccharibacteria.	**Aerobes or facultative anaerobes:** *Corynebacterium spp.*; Actinomycetota *Neisseria spp.;*, Pseudomonadota; *Streptococcus spp.*; Bacillota. *Propionibacterium spp.*; Actinomycetota.	**Aerobes or facultative anaerobes:** *Aggregatibacter actinomycetemcomitans;* Pseudomonadota [e], *Rothia spp.*; Actinomycetota, *Granulicatella spp;* Bacillota. **Obligate anaerobes:** *Prevotella spp.*; Bacteroidota, *Leptotrichia spp;* Fusobacteriota, *Fusobacteriales spp;* Fusobacteriota, *Megasphaera micronuciformis*; Bacillota, *Olsenella* spp.; Actinomycetota, *Erysipelotrichaceae ;* Bacillota, *Cryptobacterium spp.;* Actinomycetota, *Desulfovibrio spp.;* Thermodesulfobacteriota *Fretibacterium spp.;* Synergistota, *Selenomonas spp.;* Bacillota, *Treponema spp.;* Spirochaetota, *Veillonella spp.;* Bacillota.	**Aerobes or facultative anaerobes:** *Corynebacterium spp.;* Actinomycetota, *Neisseria spp.;* Pseudomonadota, *Streptococcus spp.*; Bacillota, *Haemophilus spp.;* Pseudomonadota, *Gemella spp.;* Bacillota, *Granulicatella spp.;* Bacillota.	**Obligate anaerobes:** *Prevotella spp.;* Bacteroidota[b], *Leptotrichia spp.;* Fusobacteriota[b], *Filifactor alocis;* Bacillota, *Treponema denticola;* Spirochaetota[c], *Porphyromonas spp.;* Bacteroidota[c], *Veilonella spp.;* Bacillota.	**Aerobes or facultative anaerobes:** *Corynebacterium spp.;* Actinomycetota, *Streptococcus spp.*; Bacillota. **Obligate anaerobes:** *Defluviitaleaceae spp.*; Bacillota, *Nanosynbacter oralis;* Saccharibacteria.

a - independently of RA, always higher prevalence in PD (especially severe) [19], b - present, independently of PD status [19], c - members of the „red complex bacteria", including *Porphyromonas, Tannerella* and T*reponema*, are more prevalent in new-onset RA (NORA) microbiota compared to chronic RA (CRA) patients, d - among "red complex" bacteria, *T. denticola* exhibited the highest prevalence in patients with both RA and PD [17], e - significantly more prevalent in RA patients with PD than those without PD [52], f - female RA cohort [42].

3.4 A few words about oral virome in RA patients

While exploring the oral microbiome, several studies also evaluated the co-existing virome. According to this study [61], RA patients, compared to healthy controls, are characterized by a more diverse oral viral community. Notably abundant in saliva were Callitrichine gammaherpesvirus 3, Epstein-Barr virus (EBV), Murid betaherpesvirus 8, and Suid alphaherpesvirus. Interestingly, elevated levels of EBV-infected B-cells and higher antibody titers against EBV have been also observed in RA patients [62]. Ebstein-Barr virus (EBV-1) and Cytomegalovirus (CMV) have the capability to promote bacterial colonization of the gingiva, fostering periodontal disease. PCR-based evaluations of gingival tissue revealed that EBV was present in 71-89% and CMV in 65-78% of patients with severe PD, compared to only 6% in healthy controls [63]. Additionally, Paksoy et al. [17] have reported a notable correlation between RA disease activity (DAS28-CRP) and the prevalence of EBV.

4. Dental treatment and disease-modifying anti-rheumatic drugs

Although not yet fully understood, the role of OMB in chronic inflammation is undeniable. Interventions targeting oral health such as early and regular dental treatments or prophylactic therapies, are believed to decrease the risk of developing and progressing systemic diseases like RA [33, 48, 64]. Dietary modifications, as well as probiotics and antibiotics may also modulate the course of PD and RA [65, 66]. In RA patients with chronic PD, non-surgical periodontal treatments have been shown to reduce RA activity indicators such as ESR, CRP, TNF-α, DAS28 score, as well as decreased levels of ACPA and anti-*P. gingivalis* antibodies [67, 68]. Animal models have demonstrated that oral antiseptic treatments reduce the total oral bacterial load and protect against the RA-induced periodontal bone loss, favorably altering the oral microbiome [15]. Recently, novel dental treatments such as teeth-cleaning microrobots and red-light therapy for gums have gained attention as potential technologies to enhance oral hygiene and prevent the PD and systemic bone-related diseases [69]. Pre-RA and early-RA groups may benefit most from early periodontal treatment and disease-modifying antirheumatic drugs (DMARDs), potentially preventing the progression of both PD and RA [70]. Methotrexate (MTX) has been shown in animal models to shift the oral microbiota toward a healthier composition and reduce alveolar bone loss, thereby preserving periodontal health [71]. However, combination therapies, such as MTX with other synthetic DMARDs (sDMARDs), have been associated with more advanced periodontitis stages compared to MTX monotherapy. Meanwhile, systemic corticosteroids are correlated with lower gingival index scores, but long-term use may delay healing and increase infection susceptibility [72, 73]. Sulfasalazine and hydroxychloroquine are generally considered to have minimal direct effects on periodontal tissues, while limited evidence suggests that leflunomide may have a neutral effect on periodontal health. Biologic DMARDs (bDMARDs), such as tumor necrosis factor inhibitors (e.g., infliximab, etanercept), have shown potential benefits for periodontal conditions, reducing bleeding on probing and improving gingival index, probing pocket depth, and clinical attachment level over time [73, 74]. Baricitinib, a Janus kinase (JAK) inhibitor, has also demonstrated improvements in both RA activity and periodontal status, suggesting that JAK blockade may positively influence periodontal inflammation [75]. However, it should be taken into consideration that the use of these medications is associated with an increased risk of viral, bacterial (with abscess formation) and fungal infections,. Cases of osteonecrosis of the jaw have also been reported following the use of TNF-α inhibitors [76].

The anti-inflammatory and immunomodulatory effects of RA treatments may positively influence periodontal health. However, an individualized approach considering both RA and periodontal conditions is essential. Continued research and observation will help clarify these interactions and optimize treatment strategies.

Conclusions and discussion

Rheumatoid arthritis and periodontitis share overlapping inflammatory pathways, genetic predispositions, and environmental triggers, including microbial dysbiosis. Both PD and RA can alter the immune response by modulating the cytokine profile, leading to chronic inflammation and irreversible bone destruction. Based on current knowledge, the prevalence and severity of PD is higher in RA patients, particularly those who are ACPA-positive and higher RA activity. The oral biofilm composition can modulate mucosal inflammation and trigger protein citrullination, contributing to arthritis development and progression — even in the early stages of the disease. In RA patients, systemic inflammation and a shift in the microbiome towards bacterial species associated with periodontitis may exacerbate periodontal conditions. The OMB differences are observed also in RA patients with preserved oral health. Genera such as *Porphyromonas*, *Aggregatibacter*, and *Treponema* have been positively correlated with ACPA titers and potential arthritis

exacerbation. Interestingly, it was suggested that ACPA titers may regulate the colonization of *Porphyromonas* and *Aggregatibacter*. It was observed that *B. forsythus* and *A. actinomycetemcomitans*, has the potential to mimic the repertoire of citrullinated antigens in RA joints, influencing systemic inflammation in RA. Depending on the RA activity, *Treponema spp.* and Absconditabacteriales were associated with low disease activity, *Porphyromonas spp.* with moderate disease activity, *Staphylococcus spp.* and *L. salivarius* with high disease activity. Similarly, the abundance of *F. fastidiosum*, *P. micra*, and *A. geminatus* was correlated with an increased number of swollen and tender joints.

Although the observations regarding specific bacterial species dominating the OMB in RA patients vary across studies, results consistently highlight the high abundance of periodontitis-associated species, along with a reduction in obligate anaerobic bacteria, which play a protective role in the oral cavity.

The non-invasive periodontal treatment has shown the positive impact on RA activity, underscoring the importance of regular dental check-ups as a basic recommendation for all RA patients, with particular emphasis on those in early-RA and pre-RA groups. Early periodontal treatment combined with DMARDs can prevent the progression of both PD and RA. Moreover, some anti-inflammatory treatments for RA has the potential to restore oral homeostasis. Based on current knowledge, the effects of sDMARDs and bDMARDs on periodontal health in RA patients remains scarce and requires further investigation. Nevertheless, periodontal status should be considered when planning personalized immunotherapy, particularly since changes in the OMB could serve as non-invasive biomarkers of disease progression. Future studies should aim to identify specific cellular and molecular targets to modulate immune responses, enabling treatment strategies that prevent the progression of systemic inflammation. Additional research is necessary to establish credible guidelines for application in clinical practice.

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