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Periodontitis and Rheumatoid Arthritis

Abhishek S Krishna[1], Ahalya U[1], Shaiju S Dharan[2], Amal A[3,*]

Abstract

This comprehensive review delves into the complex interplay between Periodontitis and Rheumatoid Arthritis, aiming to unravel the underlying mechanisms and shared inflammatory pathways that connect these seemingly distinct conditions. The review examines a wealth of current research, exploring how chronic periodontal inflammation may contribute to the development and progression of RA and vice versa. Furthermore, the review critically evaluates the clinical implications of this interrelation, emphasizing the need for interdisciplinary collaboration between rheumatologists and periodontal specialists. Insights from this synthesis of evidence could inform targeted therapeutic strategies and preventive measures for individuals at risk of concurrent periodontitis and rheumatoid arthritis. In summary, the review not only elucidates the complex interplay between periodontitis and rheumatoid arthritis but also underscores the importance of integrated approaches in both research and clinical management to address the multifaceted nature of these interconnected health conditions. While further studies are needed to elucidate specific mechanisms and establish causation, the existing evidence highlights the significance of collaboration between dental and rheumatological professionals for improved patient outcomes. Integrating oral health management into the holistic care of individuals with rheumatoid arthritis could pave the way for more effective preventive strategies and enhanced overall well-being.

Keywords: Periodontitis, rheumatoid arthritis, inflammatory pathways, porphyromonas gingivalis, citrullination

INTRODUCTION

Rheumatoid arthritis (RA) and Periodontitis (PD) are inflammatory chronic conditions characterized by intermittent flare-ups and flare-downs. They both involve systemic inflammatory reactions within periodontal tissues and joints, resulting in the destruction of both hard and soft tissues. Additionally, these conditions share similarities in their pathophysiological advancement, immune modulation, genetic predisposition, infiltration of inflammatory cells, and the role of enzymes and cytokines in immune responses. [1,2] Periodontitis impacts roughly half of adults and 60% of individuals aged 65 and older, with prevalence rates fluctuating based on disease severity. Rheumatoid arthritis (RA) affects 0.5%-1% of the entire population. Epidemiological investigations exploring the link between RA and PD yield varied findings, with a wide range of periodontitis prevalence among RA subjects, spanning from 28% to 85%, including 11-14% diagnosed with severe periodontitis [3,4].

***Author for Correspondence**
Amal A.
E-mail: amalapps4@gmail.com

[1]Pharm D Intern, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkara, Trivandrum, Kerala, India
[2]Principal, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkara, Trivandrum, Kerala, India
[3]Assistant Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkara, Trivandrum, Kerala, India

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The pathogenesis of PD involves a complex interplay of proinflammatory cytokines, prostaglandin E2, MMPs, nitric oxide and other inflammatory mediators.[5] Increased TNF-α, IL-1β, IL-6, IL-11, and IL-17 levels promote osteoclastogenesis by up regulating RANKL expression and lowering the synthesis of OPG (Osteoprotegerin) [6]. Furthermore, active

periodontal lesions exhibit overexpression of IL-17 and RANKL, coupled with decreased levels of anti-inflammatory cytokines like IL-10 and TGF-β1 suggesting a dysregulated immune response. This imbalance in bone metabolism not only predisposes individuals to PD but also implicates it as a potential risk factor for diseases such as rheumatoid arthritis, although consensus remains elusive [7]. The pathogenesis of rheumatoid arthritis involves complement system activation, abnormal lymphocyte responses and structural alterations that contribute to autoimmunity, immunosuppression and disease genesis [8].

Recent evidence indicates a significant link between susceptibility to rheumatoid arthritis and the HLA-DRB 1 genetic locus, attributed to citrullinated self-peptides binding to HLA-DR molecules. Porphyromonas gingivalis, a key pathogen in periodontitis and the sole known human pathogen expressing peptidyl arginine deiminase, plays a crucial role. [9] This enzyme produces citrullinated epitopes, which are targeted by anti-citrullinated protein with RA [10]. In a prospective study, individuals with RA were found to have a higher prevalence of PD, particularly among those with elevated levels of Porphyromonas gingivalis in deeper periodontal pockets compared to control subjects [11]. The immune mechanisms leading to progressive connective tissue destruction and bone loss, characteristic of rheumatoid arthritis (RA), are also prevalent in periodontal disease. PD, an infectious condition primarily caused by pathogens like Porphyromonas gingivalis, Aggregatibacter actinomycetem-comitans, Tannerella forsythia, and Treponema denticola, triggers both local and systemic immune responses. Moreover, oral bacteria DNA and antibodies found in RA patients' blood and synovial fluid suggest a possible connection between periodontitis and the onset of RA [12].

An association between PD and RA may exist beyond causal links, possibly due to shared genetic and environmental risk factors such as the expression of the MHC class II HLA-DRB 1 allele and smoking.[13,14] Despite distinct initial causes, various clinical and epidemiological studies indicate a correlation between RA and PD. Individuals with PD have an elevated risk of developing RA and vice versa; PD prevalence is at least doubled in RA patients compared to the general population.[15,16] Moreover, RA patients with PD tend to experience a more severe clinical course, regardless of age, gender, ethnicity or smoking habits compared to those without RA. Additionally, both conditions share similar mechanisms of tissue destruction mediated by inflammatory cells and proinflammatory cytokines suggesting that PD may play a role in initiating and perpetuating autoimmune inflammatory responses seen in RA [17].

ORAL HEALTH IN RA

Rheumatoid arthritis patients often exhibit various oral manifestations, such as the well-established link with Sjogren's syndrome, leading to symptoms like xerostomia. Other oral issues include temporomandibular joint disorders, ulcers induced by methotrexate, and a growing focus on periodontal disease [18,19]. It is noteworthy how frequently autoimmune illnesses, such as RA, impact the oral mucosa. While symptomatic xerostomia and secondary Sjogren's are not rare in these patients, studies vary in estimating prevalence ranging from 3-30% [20,21]. The goal of the most recent primary Sjogren's syndrome categorization criteria is to improve the precise description of the condition's prevalence, which has a major influence on people's overall health-related quality of life [22, 23] The connection between secondary sjogren's in RA and increased periodontal disease is still uncertain, with conflicting findings in studies [24].

ROLE OF P. GINGIVALIS

The effective use of antibiotics to treat bacterial anaerobic infections in cases of rheumatoid arthritis raises the possibility that bacteria may play a role in the onset of RA [25]. The presence of bacterial DNA of anaerobes and higher antibody titers against these bacteria in the serum and synovial fluid of RA patients at various stages of the disease lends credence to the theory that oral infections play a role in the etiology of RA [26, 27] [Table 1].

Table 1. Summary of papers relating to the relationship between periodontitis and rheumatoid arthritis.

SL NO:	AUTHOR	STUDY POPULATION	INCLUSION CRITERIA	RESULT
1	Yuin Li etal 2022 july 18	A total of 28 studies in which 16 case control, 4 cohort, 8 cross sectional. 4486 RA patient, 2607 control group.	Searched articles were screened based on ctiteria: Articles exploring the correlation between P. gingivalis and risk of RA.	• The pools OR indicated that exposure to P. gingivalis significantly increased the risk of RA in those people. • P. gingivalis exposure was a risk factor in RA.
2	Yiqiang Qiao etal 2020 December	13 studies including total of 706611 periodontitis patient and 349983 control subjects.	Articles having the relation between periodontitis and rheumatoid arthritis risk.	• Patient in periodontitis group had a 69% greater risk for RA than people in control group. • Periodontitis represent a risk factor for incident RA.
3	Joanna Sambor-ska-mazur etal 2020 August 31	From 190 indicated, 60 full text papers were included by the authors.	This work is a systematic review based on PubMed, with specific reference to the following key words: PAS system and periodontitis and RA; periodontal pathogen and RA; peptidylarginine deiminase and periodontitis.	• Numerous common comorbidities, bacterial, genetic, and environmental factors that modify the progression of both diseases, as well as common proinflammatory factors that affect how they develop, all contribute to the conclusion that PD and RA may have a common pathogenesis.
4	William Buwembo etal 2019 October10	3 publications were selected for systematic review and 2 for meta-analysis.	Articles providing data on both RA and periodontitis compared to controls, as well as English	• Participants with RA had higher rates of periodontal disease than did healthy controls.
			Language papers detailing original research conducted in Africa between January 2010 and December 2017, were the only ones that were chosen.	
5	Albertas Kriauciunas etal 2019 may 28	A total of 56 results were received, a review and analysis of their full texts have been carried out and 10 articles were selected.	Articles from the PubMed database that were solely full text and underwent a PRISMA analysis methodology. The papers were only five years old when they were selected.	• PPADs produced by • P. gingivalis bacterium have a significant influence on the pathogenesis of RA • Persistence of the bacteria in the oral cavity can affect the etiology of RA
6	Cleber davi del Rei Dalt ro Rosa etal 2021 september 14	7 articles for qualitative and 5 for quantitative analysis, 292 participants all have RA and periodontal disease	Articles published until April 2019 were electronically searched and screened utilizing PRISMA-compliant resources such as PubMed, MEDLINE, Scopus, and Cochrane.	• Patients suffering with RA may benefit from non-surgical periodontal therapy. • Periodontal treatment promoted significant changes in the DAS28-ESR, reducing the RA activity index.

7	Yoon young choi etal 2021	691506 individuals with 345753 patients in the periodontitis group and 345753 in the control group	Individuals in the National Health Insurance Service-Customized Research Database (NHIS-CRDB) of Korea from 2002 to 2018	• Univariate analysis revealed that the periodontitis group was more likely to develop RA than control group (hazard ratio1.10) and the multivariate analysis also showed that the group with periodontitis had a greater incidence risk of RA (adjusted hazard ratio of 1.09).
8	Stephen Renvert etal 2020	153000 population from medical records and 233 individuals with RA	RA patients had to be ≥ 61 years	• A diagnosis of periodontitis was more common in RA group (61.1%) than in the control group (33.7%)
9	Anna Svard etal 2023	196 patients with RA and 101 healthy controls.	Dental examinations were performed on patients with RA who were atleast 61years old.	• In a multivariate analysis, RA patients had a considerably greater level of salivary IgA anti-RgpB antibodiea than did healthy controls.
10	Rosamma Joseph etal 2013	100 RA patients who visited the rheumatology clinic made up the case group. The control group consisted of 112 age and gender matched patients without RA who were seen at the department of general medicine's outpatient wing.	Participants with at least ten teeth-excluding the third molars- who meet the updated criteria for RA categorization as forth by the American Rheumatism Association.	• RA participants had greater rates of both the severity and occurrence of periodontal disease when compared to non-RA subjects, indicating a significant correlation between these two chronic inflammatory disorders.

Periodontal pathogens like P. gingivalis can compromise epithelial integrity, invade human endothelial cells, and influence transcription and protein synthesis, providing a direct systemic access to the blood stream. P. gingivalis demonstrates the ability to invade primary human chondrocytes isolated from knee joints, resulting in delayed cell cycle progression and increased apoptosis in these chondrocytes [28, 29].

P. gingivalis produces cysteine endopeptidases that are specific to arginine (gingipain R) and lysine (gingipain K). These enzymes are necessary for both bacterial homeostasis and infection processes, such as the extraction of aminoacids from host proteins and the development of fimbriae [30, 31]. These gingipains, as proteolytic enzymes, contribute to virulence expression. P. gingivalis gingipains aid in the activation of proteinases such as MMP-1, MMP-3, and MMP-9 as well as the breakdown of extracellular matrix host proteins such collagen, fibronectin, and laminin, Furthermore, gingipains cause complement factor degradation and increased vascular permeability. [32,33]

The pathophysiology of RA has been linked to P. gingivalis's participation in citrullination. Proteins undergo a post-translational process called citrullination, which turns arginine residues into citrulline. P. gingivalis can colonize the oral cavity and induce a chronic inflammatory response [34, 35]. The bacterium secretes enzymes, such as peptidylarginine deiminase (PAD), which catalyses citrullination.

The infection triggers an immune response that may contribute to systemic effects. Since it produces antibodies against citrullinated proteins, citrullination is a crucial step in the development of RA (ACPAs) [36]. P. gingivalis-mediated citrullination may contribute to the generation of ACPAs, linking periodontal disease to the development or exacerbation of RA. P. gingivalis- generated citrullinated peptides may exhibit molecular mimicry with host proteins. This resemblance can provoke an immune response against self-proteins, contributing to autoimmune reactions in RA [37, 38]. Citrullinated proteins are frequently contained in the synovial tissues of RA patients. The presence of P. gingivalis and its citrullination activity in the oral cavity may influence the systemic spread of citrullinated peptides, exacerbating synovial inflammation in susceptible individuals [39, 40].

DISCUSSION

Various researches into the connection between periodontal disease and rheumatoid arthritis have reaffirmed well-established links between the two conditions [41]. Recent findings indicate that periodontal disease manifests early and severely in the onset of rheumatoid arthritis, adding weight to the argument for a potential causal or permissive relationship [42, 43]. Investigations within high-risk rheumatoid arthritis cohorts have also revealed increased exposure to periodontal bacteria before the onset of rheumatoid arthritis, along with indications of distinct bacterial colonization in early rheumatoid arthritis cases, extending beyond P. gingivalis species [44] [Figure 1].

The convergence of inflammatory cascades emerges as a central theme in the intricate interplay between periodontitis and RA. Beyond the localized effects of periodontal inflammation, recent studies emphasize the systemic outcomes, suggesting that periodontitis may serve as a catalyst for RA development or exacerbation in susceptible individuals [45]. The shared pro-inflammatory cytokines and signalling pathways offer a molecular bridge connecting these seemingly distinct pathologies. Recent clinical trials offer a glimpse into the potential therapeutic benefits of periodontal intervention in RA management. Notably, improvement in RA disease activity and reductions in inflammatory markers following targeted periodontal treatment suggest a promising avenue for integrated patient care. These findings underscore the significance of considering oral health as an integral component of the comprehensive approach to managing RA. [46, 47].

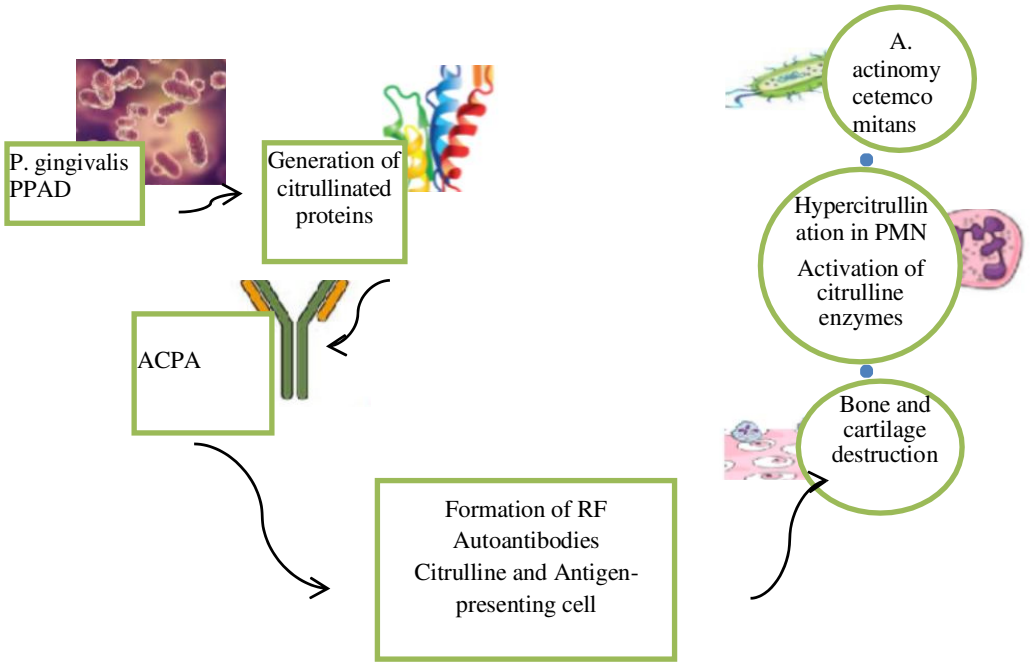

Figure 1. Mechanism of bone and cartilage destruction by P. gingivalis and A. actinomycetemcomitans.

The spotlight on Porphyromonas gingivalis takes center stage in interpreting the molecular mechanisms linking periodontitis and RA. Recent investigations highlight the presence of P. gingivalis in the synovial fluid of RA patients, raising intriguing questions about its potential role in triggering or amplifying autoimmune responses [48]. Moreover, P.gingivalis's enzymatic citrullination appears to have a role in the production of anti-citrullinated protein antibodies (ACPAs), which are a hallmark of the pathophysiology of RA. Acknowledging the bidirectional nature of the periodontitis-RA relationship is paramount. While periodontitis may contribute to the initiation or exacerbation of RA, the systemic effects of RA and its therapeutic modalities may reciprocally influence periodontal health. [49]. A holistic understanding of this dynamic interplay necessitates a multidisciplinary approach, emphasizing the integration of oral health assessments into the broader care framework for RA patients [50].

Even while there is evidence between periodontitis with rheumatoid arthritis, the exact mechanisms causing this relationship are still unclear. Therefore, it is imperative to conduct well-designed longitudinal multicentre clinical trials and additional studies with ample sample sizes. Deciphering the molecular mechanisms and clinical connections among these persistent inflammatory ailments need these investigations [51, 52]. Additionally, these studies should account for potential confounding factors, such as the medications used for treating each disease and variations in oral hygiene or smoking habits among the patients.

CONCLUSION

The extensive body of research suggests a compelling link between periodontitis and rheumatoid arthritis, emphasizing the intricate interplay between oral health and systemic inflammatory disorders. Given the similar inflammatory pathways and possible common triggers, comprehensive healthcare strategies that address periodontal and rheumatologic issues are crucial. While further studies are needed to elucidate specific mechanisms and establish causation, the existing evidence highlights the significance of collaboration between dental and rheumatological professionals for improved patient outcomes. Integrating oral health management into the holistic care of individuals with rheumatoid arthritis could pave the way for more effective preventive strategies and enhanced overall well-being.

Conflict of Interest

The authors declare no conflict of interest.

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