SVOA Dentistry
ISSN:2753-9172

ScienceVolks Open Access

Review Article

# A Review of Literature on the Relationship Between Oral Microbiota and Rheumatoid Arthritis

**Ambujakshi Manjunatha Vinayaka, BDS, DNHE, MDS[1]*, Dilip N, MBBS, (MS)[2] and Precia Meryn Jacob, BDS[3]**

[1] *Assistant professor, Department of Periodontics, PMNM Dental College and Hospital, Karnataka, India.*

[2] *Postgraduate, Department of orthopedics, BMCRI - Bangalore Medical College and Research Institute, Bangalore, Karnataka, India.*

[3] *BDS, Bapuji Dental College & Hospital, Davangere, Karnataka, India.*

***Corresponding Author:** Dr. Ambujakshi Manjunatha Vinayaka, Assistant professor, Department of Periodontics, PMNM Dental College and Hospital, Karnataka, India, Email: dravidavinu@gmail.com.*

***Received:** December 09, 2021* ***Published:** December 20, 2021*

## Abstract:

Periodontal disease (PDD) and rheumatoid arthritis (RMA) share comparative pathophysiological pathways like ongoing aggravation with resorption of the proximal bone in immunologically delicate hosts; However, PDD has a notable bacteriological etiology, and the cause of RMA remains unknown. According to some reports, an infectious agent in a vulnerable host may be the cause of RMA and dental microorganisms, in particular, periodontal bacteria, may be the causative agent of RMA infectious agents (mainly *Porphyromonas gingivalis*). PDD has been demonstrated to be more normal and extreme in patients with RMA showing a connection between the two illnesses. Antibodies against periodontal microbes have been found, and different examinations have discovered bacterial DNA in the serum and synovial liquid of patients with RMA and researched conceivable transmission courses, the presence of periodontal bacterial DNA. Overall, there is no question that RMA and PDD share comparative neurotic components, and there is generous proof for a connection between the two diseases, however more examination, including exploratory models, is expected to show the co-pathogenicity of oral microscopic organisms.

***Keywords:*** *bacterial DNA, oral bacteria, periodontal disease, rheumatoid arthritis*

## Introduction

One of the most well-known constant irresistible illnesses in people is periodontal disease (PDD), the occurrence rate of which goes from 10 to 60% in adults as per analytic measures (1). It incorporates inflammation of periodontal tissues around the teeth.In reaction to bacterial biofilms in plaque, PDD patients mobilise their guard cells (neutrophils) and produce cytokines such as interleukin 1, tumour necrosis factor, and interleukin 6. Enzymes that break down collagen (2).

Rheumatoid arthritis (RMA) is an autoimmune illness, and while hereditary factors play a part in its development, not all susceptible persons get RMA (3, 4). Synovitis is a clear indication of RMA and results in the invasion of synovial tissue into the surrounding cartilage matrix, degradation of articular cartilage, and bone loss. Environmental factors have also been proven to have a role in the genesis of RMA, which affects roughly 1% of the adult population (5). It has been proposed that microbial components, such as bacterial DNA, CpG matrices, heat shock proteins, and lipopolysaccharides (6-9), induce inflammation of the synovial membrane and adjacent soft tissues. Regarding the disease's origin, the notion that RMA is caused by an undiscovered infectious agent has been around for a long time. Infectious infections that cause arthritis are recognised to play a role in persistent RMA. Bacteria present in the gastrointestinal and urogenital tracts, such as Yersinia, Salmonella, Campylobacter, Shigella, and Chlamydia, have been linked to RMA (10-15).

The pathophysiology of cartilage and bone degradation in RMA is unclear; however, it is known that activation of MMP, cathepsin, and osteoclasts increases bone resorption (16, 17). TNF, IL1, and macrophage colony-stimulating factor (MCSF) are cytokines that are linked (18). There have recently been papers indicating a connection between RMA and Parkinson's disease (19, 20). For more over 70 years, people have thought that RMA is contagious (21). It is thought that RMA patients are directly exposed to bacteria and their virulence factors, which cause an immunological response in the synovial membrane, increasing immunocompetent T and B cells. This reaction involves neutrophils, monocytes, and lymphocytes (both T and B), which results in the production of proteinases, cytokines, and prostaglandins, which enhance osteoclast activity and bone digestion (22).

While some research shows that an infectious agent in a susceptible host is a possible cause of RMA, others do not. Others believe it is a mix of variables (23), and because the majority of the participants were researched center personnel or RMA dental clinic patients, the findings of these studies should be interpreted with care.

Those with RMA have bigger periodontal pockets (OR = 2.47) and more severe periodontitis (OR = 2.27) than patients without RMA (24). A recent case-control study of 57 RMA patients and 52 healthy people found a positive association (OR = 8.05) between RMA and PDD (25).

**PDD and RMA share a similar pathophysiology.**

Because RMA and PDD have comparable pathophysiological processes, such as chronic inflammation with nearby bone resorption, several writers have proposed that RMA and PDD are distinct manifestations of the same illness. immunologically susceptible hosts (19); nevertheless, PDD has a well-known bacterial etiology, whereas the origin of RMA is unclear. Exogenous viral agents (26) and endogenous compounds such as connective tissue proteins (collagens and proteoglycans) and altered immunoglobulins that cause autoimmune reactions have all been identified as joint stimulants (22).

Periodontal bacteria can cause immunological responses through a variety of methods, one of which is the capacity of Porphyromonas gingivalis to generate the enzyme peptidyl arginine deaminase (PAD), which results in the enzyme peptidyl arginine deaminase (PAD) (PAD). Host proteins and the potential generation of autoantigens (20). At the same time, antibodies against the heat shock proteins Prevotella nigrescens and Prevotella intermedia (HSP 70), which can elicit an immunological response to RMA (27, 28), were identified in the synovial fluid of RMA patients. Human leukocyte antigen (HLA) has been linked to RMA and Parkinson's disease.

These are significant risk factors for both illnesses, implying a tight connection. The highly polymorphic region HLADRB1 is the primary HLA marker for both disorders (29, 30). Another probable biological relationship is that IL1 cytokines are important mediators of the immune response, inflammation, and tissue death in both illnesses. Patients with RMA and Parkinson's disease showed increased levels of IL1 in synovial and gingival macrophages (31).

**Tissue destruction mechanisms in rheumatoid arthritis (RMA) and periodontal disease (PDD)**

The processes of alveolar deterioration in Parkinson's disease and the articular surface in RMA are comparable. Overproduction of different cytokines and MMPs appears to be prevalent in both illnesses (22). Both Parkinson's disease and rheumatoid arthritis (RMA) have chronically high levels of inflammatory cytokines such as IL1 and tumour necrosis factor-alpha (TNF-alpha) and low levels of immunosuppressants) (32). These cytokines, coupled with low levels of metalloproteinase inhibitor (TIMP) and high levels of MMP and prostaglandin E2 (PGE2), are linked to active disease (22).

**Periodontal disease (PDD) and rheumatoid arthritis (RMA) are associated with oral bacteria.**

The majority of clinical studies investigating viral triggers unique to RMA have employed serological techniques to determine past exposure to germs or viruses. These investigations discovered antibodies against a specific microbe or genetic material in blood or synovial fluid (33–37). Studies on the connection of cyclic pathogens with RMA have mostly focused on the identification of antibodies against different bacteria that cause periodontitis in both synovial fluid and serum, as illustrated in Figure 1. In a case-control study, serum Antibodies against periodontal pathogens were detected in patients with frequent RMA and periodontitis but not in control participants (38, 39).

**FIGURE 01 - CLINICAL STUDIES HAVE LINKED ORAL BACTERIA TO RHEUMATOID ARTHRITIS PATIENTS.**

| STUDY DESIGN | ASSAY USED | SAMPLING SITE | ASSOCIATED BACTERIA | REFERENCE |
|---|---|---|---|---|
| Case-control | Nephelometry and ELISA | Antibodies in serum | Porphyromonas gingivalis | Hitchon et al. (49) |
| Cross-sectional | PCR | Bacterial DNA in subgingival plaque, serum and synovial fluid | Prevotella intermedia, Porphyromonas gingivalis, Prevotella nigrescens | Martinez-Martinez et al. (41) |
| Case-control | ELISA | Antibodies in serum | Porphyromonas gingivalis | Mikuls et al. (40) |
| Case-control | ELISA and Immunoblotting | Antibodies in serum | Citrullinated alpha-enolase peptide and cross reactivity to Porphyromonas gingivalis | Lundberg et al. (50) |
| Case-control | Checkerboard DNA-DNA-hybridization | Bacterial DNA in serum and synovial fluid | Porphyromonas gingivalis, Tanerella forsythensis, Prevotella Intermedia | Moen et al. (39) |
| Case-control | ELISA | Antibodies in serum | Porphyromonas gingivalis, Prevotella intermedia, Prevotella melaninogenica, bacteroides, Actinobacillus actinomycetemcomitans | Ogrendik et al. (38) |
| Case-control | Agar plates | Bacterial growth | Staphylococcus aureus | Bassetti et al. (70) |
| Cross-sectional | ELISA | Antibodies in serum and synovial fluid | Bacteroides forsythus and Prevotella intermedia | Moen et al. (45) |
| Case-control | ELISA | Antibodies in serum | Actinobacillus actinomycetemcomitans | Yoshida et al. (28) |
| Case-control | Agar plates | Bacterial growth | Staphylococcus aureus | Jacobson et al. (56) |
| Case-control | ELISA | Antibodies in serum | Porphyromonas gingivalis | Yusof et al. (34) |
| Case-control | ELISA | Antibodies in serum | B. gingivalis and Aubacterium saburreum | Tolo and Jorkjend (33) |

Anti-gingivalis antibodies were more prevalent in RMA individuals compared to controls, and RMA-associated autoantibody titers and reactive protein levels were also greater in P. gingivalis-infected subjects, showing that this organism plays a role in RMA risk and disease development (40). On the other hand, it has been suggested that detecting bacterial DNA in the synovial fluid of patients with RMA is more important than detecting antibodies because this suggests that bacterial DNA is transported from the site of infection to the joints of patients with AR. focused on detecting bacterial DNA in RMA-affected joints by DNA-DNA hybridization in a checkerboard or PCR (39,41)

*P. gingivalis,* Tannerella forsythia, and P. intermedia were detected in synovial fluid samples from RMA and psoriatic arthritis patients using a staggered DNA-DNA hybrid technique (39). A recent crossover study included 19 patients with periodontitis and refractory RMA (these patients were actively treated) after treatment with disease-modifying antidiarrheal drugs (DMARD: methotrexate), sulfasalazine, leflunomide, and chloroquine). P. intermedia (89.4 percent), P. gingivalis (57.8 percent), and P. nigrescens (21.0 percent) were usually detected by PCR (41).

These two investigations indicate that chromosomal DNA from microorganisms linked with Parkinson's disease is found in the blood and synovial fluid of RMA patients. Although bacterial DNA is implicated in chronic arthritis, it is unclear whether these microbiological variables are the cause or the consequence of the illness.

**Synovitis promotes bacterial DNA uptake in the mouth.**

In the early stages of Parkinson's disease, the epithelium ulcerates, exposing the underlying connective tissue and vascular system by the subscapularis biofilm, which allows the periodontal disease to enter the bloodstream during feeding and brushing (42, 43). frequent episodes of sepsis. Sepsis occurred on an ultrasound scale of 13b, periodontal examination at 20b, and brushing at 3b (42). Finally, synovitis in RMA -affected joints has been reported to promote bacterial DNA attachment in the mouth (39). Therefore, it is unclear whether the presence of oral bacteria in the inflamed joint is the cause or the result of the inflammation.

**Bacterial DNA transport pathways There are three possible pathways for periodontal bacterial DNA transport from the periodontal site to the synovial membrane:**

1. Complete living cells cause joint infection and RMA reactivation despite rheumatic therapy.
2. By intracellular arrest of immune cells, as evidenced by the presence of phagocytic material in the synovial fluid, such as IgG, IgM, rheumatoid factor, fibrin, antinuclear factors, immune complexes, and DNA particles are examples of antinuclear factors.
3. Due to the free transport of DNA in the blood (39). Many experiments have been carried out to investigate these potential pathways. One of them is sowing synovial fluid in different cultures under aerobic and anaerobic conditions. Since no bacterial growth was observed, these results indicate that there were no viable bacterial cells in the tested samples. Isolated whole blood leukocytes were also tested for bacterial DNA by PCR, and none of the samples tested positive for any of the periodontal species studied, indicating that DNA did not travel from tooth sites to joints in immune cells. There are two possible mechanisms by which bacterial DNA appears to be transported as free DNA (41).

**Rheumatoid Arthritis and Porphyromonas gingivalis (RMA)**

Patients with quickly progressing periodontitis, periodontitis, chronic periodontitis, and the control group, on the other hand, were found to have the same amount of IgG antibodies to P. gingivalis in serum (34). They observed no changes between RMA patients and controls, which might be attributed to the study's limited sample size and methodology. (3.4). RMA, as previously stated, is an autoimmune illness marked by an immune reaction to citrullinated proteins. Citrullination, commonly known as deamination, is an arginine side chain enzyme-catalyzed alteration of peptidyl arginine deaminase (PAD). The protein's structure, antigenicity, and function can all be altered by this post-translational alteration.

Cyclic citrullinated antibodies to pepsin have been linked to RMA and are utilized in clinical diagnosis. Citrullinated antigens found in the joints include fibrinogen, vimentin, type II collagen, and alpha-enolase. 2. (46) P. gingivalis generates a microbial enzyme that is comparable to the human PAD enzyme. It has been proposed that antigens of this enzyme promote the formation of rheumatoid factor and local inflammation of the gums and synovial membranes as a risk factor for the development of RMA (20).

PAD causes the synovium to produce potential AR autoantigens such as fibrin, which, when combined with MHC molecules and antigen-presenting cells, results in the development of antibodies capable of resisting CCP (47).

It has been proposed that the immunological response to *P. gingivalis* may decrease immune tolerance to citrullinated antigens (48, 49). It has also been observed that there is sequence similarity and cross-reactivity with bacterial enolase (50). Several animal model experiments have been conducted to investigate the connection between *P. gingivalis* and RMA. A recent study found that injecting heat-killed *P. gingivalis* into the backs of DA rats increased the development of arthritis as assessed by leg edema (51). This work convincingly established that a preexisting chronic inflammatory lesion produced by P. gingivalis leads to the development of arthritis in an animal model (51).

Another study utilized *P gingivalis* and *Aggregatibacter actinomyctemcomitans* to produce periodontal disease in rats. This reaction was linked to increased levels of TNF, IL1, IL17, MMP13, and RANKL in a genetically vulnerable mouse strain, showing that a shared functional and hyperinflammatory genotype obstructs innate and adaptive immune responses (31). P. gingivitis impacts the development of the human chondrocyte cell cycle and apoptosis is another proposed method of connection between the two. *P. gingivalis* has been found to adhere to and infect primary human chondrocytes, affecting cell cycle development.

Gingival illness may contribute to the tissue damage seen in RMA in this situation (52). P. gingivalis has also been found to promote apoptosis and the breakdown of the extracellular matrix into macromolecule fragments.

Fibronectin fragments are linked with illness severity in both RMA and Parkinson's disease, although the mechanism is unclear, as illustrated in Figure 2. (53). Interleukin 17 (IL17), a pro-inflammatory cytokine released by the CD4 (+) Th17 subpopulation, has been shown to accelerate bone degradation in RMA and also plays a crucial role in the host's innate immune response against infections such as P. gingivalis (54).

**FIGURE 02 - IN VITRO STUDIES SHOW A LINK BETWEEN PORPHYROMONAS GINGIVALIS AND ARTHRITIS.**

| FOCUS | ASSAY | ASSOCIATED BACTERIA | SAMPLE | REFERENCE |
|---|---|---|---|---|
| Protein citrullination by P. gingivalis and breaking tolerance in RA | Immunoblotting Mass spectrometry | Porphyromonas gingivalis | Cell culture | Wegner et al. (46) |
| P gingivalis infection and its effects on cell cycle progression and apoptosis of human articular chondrocytes | Scanning electron microscopy Double immunofluorescence Cytometry TUNEL Western blot analysis | Porphyromonas gingivalis | Cell culture | Pischon et al. (52) |
| Exacerbation of action of a proapoptotic fibronectin on nitric oxide by bacteria | Western blot analysis Immunofluorescence. ELISA | Porphyromonas gingivalisStreptococcus mutans | Cell culture | Ghosh et al., 2008. (53) |
| Hyperinflammatory genotype and functional interferences in innate and adaptive immune responses | ELISA | Porphyromonas gingivalisAggregatibacter actinomycetemcomitans | Mice | Trombone et al. (31) |

Although recent evidence suggests that Th17 cells are more osteoblastic than other T helper subsets such as Th1 or Th2 and that inhibiting IL17 signaling before *P. gingivalis* infection increases susceptibility to periodontal bone loss (55), in mice, an increase in periodontal bone tissue is observed with IL17RA deficiency. destruction, suggesting an osteoprotective role for IL17 (54). Finally, IgG antibodies to *Aggregatibacter* actinomycetemcomitans' 40 kDa heat shock protein were substantially greater in RMA sera than in healthy control sera (28).

**Periodontal infection control reduces the incidence of active rheumatoid arthritis (RMA)**

Recent research indicates that decreasing blood TNF levels can help fight infection and periodontitis by removing calculus, straightening roots, and practicing good hygiene (58). Furthermore, recent clinical trials have indicated that Parkinson's disease therapy might have a significant influence on the severity of RMA (58-60).

**Dual-use biologics**

Tetracyclines, nonsteroidal anti-inflammatory medications (NSAIDs), and bisphosphonates (61) are used to treat both RMA and Parkinson's disease.

Tetracycline is effective against both gram-negative and gram-positive bacteria and has been found to decrease the action of MMP collagenase (20). Both of these illnesses are caused by enzymes that destroy the bone. MMPs have been demonstrated to enhance the activity of synovial fluid in RMA patients (62).

As a result, tetracyclines may be helpful in individuals with RMA and Parkinson's disease because they are effective against bacteria linked to periodontitis and perhaps RMA, and they also decrease bone degradation by blocking MMP (63, 64).

NSAIDs work by blocking cyclooxygenase, an enzyme responsible for prostaglandin production. Prostaglandins, which are key mediators of bone resorption in periodontitis, are abundant in periodontal tissues (65). NSAIDs are often used in the treatment of RMA to decrease pain and inflammation. NSAIDs can directly inhibit neutrophil activity and function (66), as well as the production of TNF from monocytes and natural killer cells (67). These cyclooxygenase-independent actions may contribute to the efficacy of NSAIDs in the treatment of RMA.

## Conclusion

There is no question that PDD and RMA share many pathological characteristics. Over the last few decades, periodontal investigations have found significant evidence of a link between elevated blood antibodies to periodontal microorganisms and disease severity (34, 45, 68, 69).

Simultaneously, several studies have used molecular biology techniques to identify cyclic pathogens in serum and synovial fluid samples from RMA patients (39, 41); however, the current presence of microorganisms (viable replicators) or bacterial DNA, despite new data, suggests a strong association between disease severity and Parkinson's disease severity in RMA patients, but this association is not conclusive. As a result, experimental models, particularly animal models, must be developed.

## References


1. Papapanou PN. Periodontal diseases: epidemiology. *Ann Periodontol*. 1996;1(1):1-36. doi:10.1902/annals.1996.1.1.1

2. Takashiba S, Naruishi K, Murayama Y. Perspective of cytokine regulation for periodontal treatment: fibroblast biology. J Periodontol. 2003;74(1):103-110. doi:10.1902/jop.2003.74.1.103

3. Silman AJ, MacGregor AJ, Thomson W, et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. *Br J Rheumatol*. 1993;32(10):903-907. doi:10.1093/rheumatology/32.10.903

4. Bellamy N, Duffy D, Martin N, Mathews J. Rheumatoid arthritis in twins: a study of aetiopathogenesis based on the Australian Twin Registry. Ann Rheum Dis. 1992;51(5):588-593. doi:10.1136/ard.51.5.588

5. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. *Autoimmun Rev*. 2005;4(3):130-136. doi:10.1016/j.autrev.2004.09.002

6. Albani S, Carson DA, Roudier J. Genetic and environmental factors in the immune pathogenesis of rheumatoid arthritis. Rheum Dis Clin North Am. 1992;18(4):729-740.

7. Deng GM, Tarkowski A. The role of bacterial DNA in septic arthritis. Int J Mol Med. 2000;6(1):29-33. doi:10.3892/ijmm.6.1.29

8. Deng GM, Tarkowski A. The features of arthritis induced by CpG motifs in bacterial DNA. Arthritis Rheum. 2000;43(2):356-364. doi:10.1002/1529-0131(200002)43:2<356::AID-ANR15>3.0.CO;2-J

9. Klareskog L, Padyukov L, Lorentzen J, Alfredsson L. Mechanisms of disease: Genetic susceptibility and environmental triggers in the development of rheumatoid arthritis. *Nat Clin Pract Rheumatol*. 2006;2(8):425-433. doi:10.1038/ncprheum0249

10. Bas S, Griffais R, Kvien TK, Glennås A, Melby K, Vischer TL. Amplification of plasmid and chromosome Chlamydia DNA in synovial fluid of patients with reactive arthritis and undifferentiated seronegative oligoarthropathies. *Arthritis Rheum*. 1995;38(7):1005-1013. doi:10.1002/art.1780380718

11. Branigan PJ, Gérard HC, Hudson AP, Schumacher HR Jr, Pando J. Comparison of synovial tissue and synovial fluid as the source of nucleic acids for detection of Chlamydia trachomatis by polymerase chain reaction [published correction appears in Arthritis Rheum 1997 Apr;40(4):782] [published correction appears in Arthritis Rheum 1997 Feb;40(2):387]. *Arthritis Rheum*. 1996;39(10):1740-1746. doi:10.1002/art.1780391018

12. Hyrich KL, Inman RD. Infectious agents in chronic rheumatic diseases. *Curr Opin Rheumatol*. 2001;13(4):300-304. doi:10.1097/00002281-200107000-00010

13. Cuchacovich R, Japa S, Huang WQ, et al. Detection of bacterial DNA in Latin American patients with reactive arthritis by a polymerase chain reaction and sequencing analysis. *J Rheumatol*. 2002;29(7):1426-1429.

14. Zhang X, Pacheco-Tena C, Inman RD. Microbe hunting in the joints. *Arthritis Rheum*. 2003;49(4):479-482. doi:10.1002/art.11186

15. Cox CJ, Kempsell KE, Gaston JS. Investigation of infectious agents associated with arthritis by reverse transcription PCR of bacterial rRNA. *Arthritis Res Ther*. 2003;5(1): R1-R8. doi:10.1186/ar602

16. Woolley DE, Tetlow LC. Observations on the microenvironmental nature of cartilage degradation in rheumatoid arthritis. *Ann Rheum Dis*. 1997;56(3):151-161. doi:10.1136/ard.56.3.151

17. Haynes DR, Crotti TN, Loric M, Bain GI, Atkins GJ, Findlay DM. Osteoprotegerin and receptor activator of nuclear factor kappaB ligand (RANKL) regulate osteoclast formation by cells in the human rheumatoid arthritic joint. *Rheumatology (Oxford)*. 2001;40(6):623-630. doi:10.1093/rheumatology/40.6.623

18. Chu CQ, Field M, Allard S, Abney E, Feldmann M, Maini RN. Detection of cytokines at the cartilage/pannus junction in patients with rheumatoid arthritis: implications for the role of cytokines in cartilage destruction and repair. *Br J Rheumatol*. 1992;31(10):653-661. doi:10.1093/rheumatology/31.10.653

19. Greenwald RA, Kirkwood K. Adult periodontitis as a model for rheumatoid arthritis (with emphasis on treatment strategies). *J Rheumatol*. 1999;26(8):1650-1653.

20. Rosenstein ED, Greenwald RA, Kushner LJ, Weissmann G. Hypothesis: the humoral immune response to oral bacteria provides a stimulus for the development of rheumatoid arthritis. *Inflammation*. 2004;28(6):311-318. doi:10.1007/s10753-004-6641-z

21. Ebringer A, Wilson C. HLA molecules, bacteria and autoimmunity. *J Med Microbiol*. 2000;49(4):305-311. doi:10.1099/0022-1317-49-4-305

22. Bartold PM, Marshall RI, Haynes DR. Periodontitis and rheumatoid arthritis: a review. *J Periodontol*. 2005;76(11 Suppl):2066-2074. doi:10.1902/jop.2005.76.11-S.2066

23. Carty SM, Snowden N, Silman AJ. Should infection still be considered as the most likely triggering factor for rheumatoid arthritis?. *J Rheumatol*. 2003;30(3):425-429.

24. Mercado F, Marshall RI, Klestov AC, Bartold PM. Is there a relationship between rheumatoid arthritis and periodontal disease?. *J Clin Periodontol*. 2000;27(4):267-272. doi:10.1034/j.1600-051x.2000.027004267.x

25. Pischon N, Pischon T, Kröger J, et al. Association among rheumatoid arthritis, oral hygiene, and periodontitis. *J Periodontol*. 2008;79(6):979-986. doi:10.1902/jop.2008.070501

26. Carty SM, Snowden N, Silman AJ. Should infection still be considered as the most likely triggering factor for rheumatoid arthritis?. *Ann Rheum Dis*. 2004;63 Suppl 2(Suppl 2):ii46-ii49. doi:10.1136/ard.2004.028241

27. Schett G, Redlich K, Xu Q, et al. Enhanced expression of heat shock protein 70 (hsp70) and heat shock factor 1 (HSF1) activation in rheumatoid arthritis synovial tissue. Differential regulation of hsp70 expression and hsf1 activation in synovial fibroblasts by proinflammatory cytokines, shear stress, and anti-inflammatory drugs. *J Clin Invest*. 1998;102(2):302-311. doi:10.1172/JCI2465

28. Yoshida A, Nakano Y, Yamashita Y, et al. Immunodominant region of Actinobacillus actinomycetemcomitans 40-kilodalton heat shock protein in patients with rheumatoid arthritis. *J Dent Res*. 2001;80(1):346-350. doi:10.1177/00220345010800010901

29. Weyand CM, Goronzy JJ. Association of MHC and rheumatoid arthritis. HLA polymorphisms in phenotypic variants of rheumatoid arthritis. *Arthritis Res*. 2000;2(3):212-216. doi:10.1186/ar90

30. Marotte H, Farge P, Gaudin P, Alexandre C, Mougin B, Miossec P. The association between periodontal disease and joint destruction in rheumatoid arthritis extends the link between the HLA-DR shared epitope and severity of bone destruction. *Ann Rheum Dis*. 2006;65(7):905-909. doi:10.1136/ard.2005.036913

31. Trombone AP, Claudino M, Colavite P, et al. Periodontitis and arthritis interaction in mice involves a shared hyperinflammatory genotype and functional immunological interferences. *Genes Immun*. 2010;11(6):479-489. doi:10.1038/gene.2010.13

32. Arend WP, Dayer JM. Cytokines and cytokine inhibitors or antagonists in rheumatoid arthritis. *Arthritis Rheum*. 1990;33(3):305-315. doi:10.1002/art.1780330302

33. Tolo K, Jorkjend L. Serum antibodies and loss of periodontal bone in patients with rheumatoid arthritis. *J Clin Periodontol*. 1990;17(5):288-291. doi:10.1111/j.1600-051x.1990.tb01091.x

34. Yusof Z, Porter SR, Greenman J, Scully C. Levels of serum IgG against Porphyromonas gingivalis in patients with rapidly progressive periodontitis, rheumatoid arthritis, and adult periodontitis. *J Nihon Univ Sch Dent*. 1995;37(4):197-200. doi:10.2334/josnusd1959.37.197

35. Wilbrink B, van der Heijden IM, Schouls LM, et al. Detection of bacterial DNA in joint samples from patients with undifferentiated arthritis and reactive arthritis, using polymerase chain reaction with universal 16S ribosomal RNA primers. *Arthritis Rheum*. 1998;41(3):535-543. doi:10.1002/1529-0131(199803)41:3<535::AID-ART20>3.0.CO;2-4

36. Braun J, Tuszewski M, Eggens U, et al. Nested polymerase chain reaction strategy simultaneously targeting DNA sequences of multiple bacterial species in inflammatory joint diseases. I. Screening of synovial fluid samples of patients with spondyloarthropathies and other arthritides. *J Rheumatol*. 1997;24(6):1092-1100.

37. Gérard HC, Wang Z, Wang GF, et al. Chromosomal DNA from a variety of bacterial species is present in synovial tissue from patients with various forms of arthritis. *Arthritis Rheum*. 2001;44(7):1689-1697. doi:10.1002/1529-0131(200107)44:7<1689::AID-ART293>3.0.CO;2-K

38. Ogrendik M, Kokino S, Ozdemir F, Bird PS, Hamlet S. Serum antibodies to oral anaerobic bacteria in patients with rheumatoid arthritis. *MedGenMed*. 2005;7(2):2. Published 2005 Jun 16.

39. Moen K, Brun JG, Valen M, et al. Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. *Clin Exp Rheumatol*. 2006;24(6):656-663.

40. Mikuls TR, Payne JB, Reinhardt RA, et al. Antibody responses to Porphyromonas gingivalis (P. gingivalis) in subjects with rheumatoid arthritis and periodontitis. *Int Immunopharmacol*. 2009;9(1):38-42. doi:10.1016/j.intimp.2008.09.008

41. Martinez-Martinez RE, Abud-Mendoza C, Patiño-Marin N, Rizo-Rodríguez JC, Little JW, Loyola-Rodríguez JP. Detection of periodontal bacterial DNA in serum and synovial fluid in refractory rheumatoid arthritis patients. *J Clin Periodontol*. 2009;36(12):1004-1010. doi:10.1111/j.1600-051X.2009.01496.x

42. Kinane DF, Riggio MP, Walker KF, MacKenzie D, Shearer B. Bacteraemia following periodontal procedures. *J Clin Periodontol*. 2005;32(7):708-713. doi:10.1111/j.1600-051X.2005.00741.x

43. de Pablo P, Chapple IL, Buckley CD, Dietrich T. Periodontitis in systemic rheumatic diseases. *Nat Rev Rheumatol*. 2009;5(4):218-224. doi:10.1038/nrrheum.2009.28

44. Pierce DL, Nishiyama S, Liang S, et al. Host adhesive activities and virulence of novel fimbrial proteins of Porphyromonas gingivalis. *Infect Immun*. 2009;77(8):3294-3301. doi:10.1128/IAI.00262-09

45. Moen K, Brun JG, Madland TM, Tynning T, Jonsson R. Immunoglobulin G and A antibody responses to Bacteroides forsythias and Prevotella intermedia in sera and synovial fluids of arthritis patients. *Clin Diagn Lab Immunol*. 2003;10 (6):1043-1050. doi:10.1128/cdli.10.6.1043-1050.2003

46. Wegner N, Lundberg K, Kinloch A, et al. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. *Immunol Rev*. 2010;233(1):34-54. doi:10.1111/j.0105-2896.2009.00850.x

47. Wegner N, Wait R, Sroka A, et al. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis. *Arthritis Rheum*. 2010;62(9):2662-2672. doi:10.1002/art.27552

48. Liao F, Li Z, Wang Y, Shi B, Gong Z, Cheng X. Porphyromonas gingivalis may play an important role in the pathogenesis of periodontitis-associated rheumatoid arthritis. *Med Hypotheses*. 2009;72(6):732-735. doi:10.1016/ j.mehy.2008.12.040

49. Hitchon CA, Chanda F, Ferucci ED, et al. Antibodies to porphyromonas gingivalis are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. *J Rheumatol*. 2010;37(6):1105-1112. doi:10.3899/jrheum.091323

50. Lundberg K, Kinloch A, Fisher BA, et al. Antibodies to citrullinated alpha-enolase peptide 1 are specific for rheumatoid arthritis and cross-react with bacterial enolase. *Arthritis Rheum*. 2008;58(10):3009-3019. doi:10.1002/art.23936

51. Bartold PM, Marino V, Cantley M, Haynes DR. Effect of Porphyromonas gingivalis-induced inflammation on the development of rheumatoid arthritis. *J Clin Periodontol*. 2010;37(5):405-411. doi:10.1111/j.1600-051X.2010.01552.x

52. Pischon N, Röhner E, Hocke A, et al. Effects of Porphyromonas gingivalis on cell cycle progression and apoptosis of primary human chondrocytes. *Ann Rheum Dis*. 2009;68(12):1902-1907. doi:10.1136/ard.2008.102392

53. Ghosh A, Park JY, Fenno C, Kapila YL. Porphyromonas gingivalis, gamma interferon, and a proapoptotic fibronectin matrix form a synergistic trio that induces c-Jun N-terminal kinase 1-mediated nitric oxide generation and cell death. *Infect Immun*. 2008;76(12):5514-5523. doi:10.1128/IAI.00625-08

54. Yu JJ, Ruddy MJ, Conti HR, Boonanantanasarn K, Gaffen SL. The interleukin-17 receptor plays a gender-dependent role in host protection against Porphyromonas gingivalis-induced periodontal bone loss. *Infect Immun*. 2008;76(9):4206 -4213. doi:10.1128/IAI.01209-07

55. Yu JJ, Gaffen SL. Interleukin-17: a novel inflammatory cytokine that bridges innate and adaptive immunity. *Front Biosci*. 2008;13:170-177. Published 2008 Jan 1. doi:10.2741/2667

56. Jacobson JJ, Patel B, Asher G, Woolliscroft JO, Schaberg D. Oral staphylococcus in older subjects with rheumatoid arthritis. *J Am Geriatr Soc*. 1997;45(5):590-593. doi:10.1111/j.1532-5415.1997.tb03092.x

57. Jackson MS, Bagg J, Gupta MN, Sturrock RD. Oral carriage of staphylococci in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 1999;38(6):572-575. doi:10.1093/rheumatology/38.6.572

58. Ortiz P, Bissada NF, Palomo L, et al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *J Periodontol*. 2009;80(4):535-540. doi:10.1902/ jop.2009.080447

59. Ribeiro J, Leão A, Novaes AB. Periodontal infection as a possible severity factor for rheumatoid arthritis. *J Clin Periodontol*. 2005;32(4):412-416. doi:10.1111/j.1600-051X.2005.00689.x

60. Al-Katma MK, Bissada NF, Bordeaux JM, Sue J, Askari AD. Control of periodontal infection reduces the severity of active rheumatoid arthritis. *J Clin Rheumatol*. 2007;13(3):134-137. doi:10.1097/RHU.0b013e3180690616

61. Modi DK, Chopra VS, Bhau U. Rheumatoid arthritis and periodontitis: biological links and the emergence of dual-purpose therapies. *Indian J Dent Res*. 2009;20(1):86-90. doi:10.4103/0970-9290.49070

62. Fiedorczyk M, Klimiuk PA, Sierakowski S, Gindzienska-Sieskiewicz E, Chwiecko J. Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with early rheumatoid arthritis. *J Rheumatol*. 2006;33(8):1523-1529.

63. Stone M, Fortin PR, Pacheco-Tena C, Inman RD. Should tetracycline treatment be used more extensively for rheumatoid arthritis? Meta-analysis demonstrates clinical benefit with reduction in disease activity. *J Rheumatol*. 2003;30 (10):2112-2122.

64. Sorsa T, Tjäderhane L, Konttinen YT, et al. Matrix metalloproteinases: contribution to pathogenesis, diagnosis, and treatment of periodontal inflammation. *Ann Med*. 2006;38(5):306-321. doi:10.1080/07853890600800103

65. Salvi GE, Williams RC, Offenbacher S. Nonsteroidal anti-inflammatory drugs as adjuncts in the management of periodontal diseases and peri-implantitis. *Curr Opin Periodontol*. 1997;4:51-58.

66. Pillinger MH, Capodici C, Rosenthal P, et al. Modes of action of aspirin-like drugs: salicylates inhibit Erk activation and integrin-dependent neutrophil adhesion. *Proc Natl Acad Sci U S A*. 1998;95(24):14540-14545. doi:10.1073/pnas.95.24.14540

67. Lavagno L, Gunella G, Bardelli C, et al. Anti-inflammatory drugs and tumor necrosis factor-alpha production from monocytes: role of transcription factor NF-kappa B and implication for rheumatoid arthritis therapy. *Eur J Pharmacol*. 2004;501(1-3):199-208. doi:10.1016/j.ejphar.2004.07.101

68. Albandar JM, DeNardin AM, Adesanya MR, Diehl SR, Winn DM. Associations between serum antibody levels to periodontal pathogens and early-onset periodontitis. *J Periodontol*. 2001;72(11):1463-1469. doi:10.1902/jop.2001.72.11.1463

69. Ebersole JL, Cappelli D, Mathys EC, et al. Periodontitis in humans and non-human primates: oral-systemic linkage inducing acute-phase proteins. *Ann Periodontol*. 2002;7(1):102-111. doi:10.1902/annals.2002.7.1.102

70. Bassetti S, Wasmer S, Hasler P, et al. Staphylococcus aureus in patients with rheumatoid arthritis under conventional and anti-tumor necrosis factor-alpha treatment. *J Rheumatol*. 2005;32(11):2125-2129.

**Citation:** Vinayaka AM, Dilip N, Jacob PM. "A Review of Literature on the Relationship Between Oral Microbiota and Rheumatoid Arthritis". SVOA Dentistry 3:1 (2022) Pages 13-20.