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Rheumatoid arthritis and the role of oral bacteria

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Rheumatoid arthritis (RA) and periodontal disease (PD) have shown similar physiopathologic mechanisms such as chronic inflammation with adjacent bone resorption in an immunogenetically susceptible host; however, PD has a well-recognized bacterial etiology while the cause of RA is unclear. Some reports have indicated that an infectious agent in a susceptible host could be one possible trigger factor for RA, and it has been suggested that oral microorganisms, specialty periodontal bacteria could be the infectious agent (mainly *Porphyromonas gingivalis*). It has been reported that PD is more frequent and more severe in patients with RA, suggesting a positive association between both diseases. There have been reports regarding the detection of antibodies against periodontal bacteria while other studies have identified periodontal bacterial DNA in serum and synovial fluid of RA patients and have explored the possible pathways of transport of periodontal bacterial DNA. In conclusion, there is no question that RA and PD have pathologic features in common and there is strong evidence of an association between both diseases, but further studies, including experimental models, are needed to demonstrate the arthritogenicity of oral microorganisms.

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

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Periodontal disease (PD) is one of the most common chronic disorders of infectious origin known in humans with a prevalence of 10–60% in adults depending on the diagnostic criteria (1). It includes gingivitis, an inflammatory condition of the soft tissues surrounding the tooth and periodontitis that involves loss of alveolar bone. Patients affected by PD respond to bacterial dental plaque biofilm by mobilizing their defensive cells and releasing cytokines like interleukin-1β, tumor necrosis factor-α, and interleukin-6, which lead to tissue destruction by stimulating the production of the collagenolytic enzymes: matrix metalloproteinases (MMPs) (2).

Rheumatoid arthritis (RA) is considered an autoimmune disease and while genetic factors are important in the development of the disease, not all susceptible patients develop RA (3, 4). RA is characterized by inflammation of the synovial membrane, leading to an invasion of the synovial tissue into the adjacent cartilage matrix with degradation of the articular cartilage and bone destruction. It affects approximately 1% of the adult population and environmental factors have also been shown to play a role in the etiology of RA (5). It has been proposed that synovial and adjacent soft tissue inflammation may be initiated by a number of microbial factors, including bacterial DNA, CpG motifs, heat shock proteins, and lipopolysaccharides (6–9). The thought that RA may be triggered by an unknown infectious agent has been a longstanding concept in its pathogenesis. It has been well established that in the case of refractory RA, infectious agents triggering joint inflammation are involved. Gastrointestinal and urogenital bacterial species such as *Yersinia*, *Salmonella*, *Camphylobacter*, *Shigella*, and *Chlamydia* have all been associated with RA (10–15).

The pathophysiological mechanisms of cartilage and bone destruction in RA are not exactly understood. However, it is known that MMPs, cathepsins, and osteoclast activation contribute to bone resorption (16, 17). A number of cytokines like TNF-α, IL-1, and macrophage colony-stimulating factor (MCSF) are also involved (18).

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Epidemiological association between rheumatoid arthritis (RA) and periodontal disease (PD)

There have been recent reports suggesting a significant association between RA and PD (19, 20). The hypothesis that RA is an infectious disease has been postulated for over 70 years (21). It is proposed that RA patients have direct contact with microorganisms and their virulence factors, which activate an immune response in the synovial membrane with the accumulation of immunocompetent T- and B-cells. This reaction is mediated by neutrophils, monocytes, and lymphocytes (both T and B), leading to the release of proteinases, cytokines, and prostaglandins that stimulate osteoclast activity and bone resorption (22). While some reports have indicated that an infectious agent in a susceptible host could be one possible trigger factor for RA (23), the published studies vary widely with respect to study design and methods used for the diagnoses of RA and PD, which in turn make it difficult to ascertain the association between RA and PD. The clinical designs most commonly used were case-control and cross-sectional studies with the main concern being the criteria used to define control subjects. Most of the volunteers were recruited from the staff at the study centers or were patients attending dental clinics, such that the results of these studies need to be treated with caution.

Some prospective clinical trials have shown that individuals with RA are more likely to experience moderate to severe PD compared with healthy subjects, while others have reported a high incidence of RA in patients with periodontitis. There is evidence that RA patients have deeper periodontal pockets (OR=2.47) and greater severity of periodontitis (OR=2.27) (24). In a recent case-control study that involved 57 RA patients and 52 healthy subjects, RA patients showed a positive association (OR=8.05) with PD (25).

Common pathophysiologic mechanisms

The fact that RA and PD have similar physiopathologic mechanisms, such as chronic inflammation with adjacent bone resorption, has led some authors to suggest that RA and PD are a variety of the same disease. Both are chronic inflammatory reactions in an immunogenetically susceptible host (19); however, PD has a well-recognized bacterial etiology while on the other hand the cause of RA is unclear. It has been accepted that many different arthritogenic stimuli exist that could include exogenous infectious factors (26) or endogenous substances such as connective tissue proteins (collagens and proteoglycans) and altered immunoglobulins resulting in an autoimmune response (22).

Periodontal bacteria are able to activate immunological responses by different mechanisms; one such mechanism includes the ability of *Porphyromonas gingivalis* to produce a peptidyl arginine deaminase enzyme (PAD), which leads to citrullination of host proteins and the production of putative autoantigens (20). At the same time, antibodies against heat shock proteins (hsp 70) of *Prevotella nigrescens* and *Prevotella intermedia* have been found in synovial fluid of patients with RA possibly triggering an immune response (27, 28). It has also been reported that human leukocyte antigen (HLA) genes are directly associated with RA and PD. These are powerful risk factors for both diseases, further suggesting a close connection. The main HLA marker for both diseases is the highly polymorphic HLA-DRB1 locus (29, 30).

Another possible biological link is the fact that IL-1 cytokines are the main mediators of the immune response, inflammation, and tissue destruction in both diseases. There are increased levels of IL-1β in synovial tissue macrophages and gingival crevicular fluid in patients with RA and PD (22). Studies in animal models have shown high levels of tissue MMPs, tumor necrosis factor-α, and IL-1β in both diseases indicating a similar pattern of tissue destruction (31).

Mechanisms of tissue destruction in rheumatoid arthritis (RA) and periodontal disease (PD)

The mechanisms of alveolar bone destruction in PD and articular surfaces in RA are similar. There is an overproduction of a variety of cytokines and MMPs that appear to be common in both diseases (22). PD and RA both have persistent high levels of proinflammatory cytokines, including IL-1β and tumor necrosis factor-alpha (TNF-α), and low levels of cytokines that suppress the immunoinflammatory response such as IL-10 and transforming growth factor-β (TGF-β) (32). These cytokines, together with low levels of metalloproteinases inhibitors (TIMPs), and high levels of MMPs and prostaglandin E_2 (PGE_2) are associated with disease activity (22).

The link between periodontal disease (PD) and rheumatoid arthritis (RA): oral bacteria

Most of the clinical studies that have implicated specific infective triggers for RA have relied on serological methods to detect prior exposure to bacteria or to viruses. These studies have either detected antibodies against a target microorganism or identified genetic material in blood or synovial fluid (33–37). There have been studies exploring the association of periodontopathogenic bacteria with RA, these were mainly focused on the detection of antibodies against the different bacteria associated with periodontitis in both synovial fluid and serum, Table 1. In a case-control study, serum antibodies against disease-producing periodontal bacteria were identified more frequently in subjects affected by RA and periodontitis than control subjects (38, 39). In particular anti-*P. gingivalis*, antibodies have been reported to be more frequent in RA subjects compared with controls and that

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Table 1. Oral bacteria associated to rheumatoid arthritis patients in clinical studies

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)

the titer of RA-related autoantibodies and C-reactive protein concentrations are also higher in individuals infected with *P. gingivalis* suggesting that this organism plays a role in disease risk and progression in RA (40).

On the other hand, it has been proposed that the detection of bacterial DNA in the synovial fluid of RA patients is more important than the detection of antibodies as it suggests the transport of bacterial DNA from sites of infection to the joints of RA patients. Recently, there have been reports that have focused on the detection of bacterial DNA in RA-affected joints using checkerboard DNA–DNA-hybridization or PCR assays (39, 41). In this context, it has been reported that *P. gingivalis*, *Tannerella forsythia*, and *P. intermedia* have been identified in synovial fluid samples from RA and psoriatic arthritis patients using the checkerboard DNA–DNA-hybridization assay (39). A recent cross-sectional study involving 19 subjects with periodontitis and refractory RA (these patients received intensive treatment with disease-modifying antirheumatic drugs DMARDs: methotrexate, sulfasazine, leflunomide, and chloroquine) has shown that *P. intermedia* (89.4%), *P. gingivalis* (57.8%), and *P. nigrescens* (21.0%), were frequently detected with PCR (41). These two studies clearly demonstrate that chromosomal DNA from bacteria associated with PD is present in serum and synovial fluid from patients with RA. Although bacterial DNA might be associated with chronic inflammation of the joints, it remains to be determined whether these microbial factors are a cause or are a result of the disease.

Synovial inflammation facilitates trapping of oral bacterial DNA

In the early stages of PD, the epithelium ulcerates to expose the underlying connective tissues and vasculature to the subgingival biofilm, this then provides for the entry of periodontopathic into the bloodstream during eating and brushing (42, 43). It is well established that patients affected by PD have frequent episodes of bacteremia. The frequency of bacteremia after ultrasonic scaling is 13%, after periodontal probing 20%, and after tooth brushing it is 3% (42).

Finally, it has been reported that synovial inflammation in the joint affected by RA favors trapping of oral bacterial DNAs (39). Hence, it is unknown whether the presence of oral bacteria in the inflamed joint is a cause or a result of the inflammation.

Pathways of transport of bacterial DNA

There could be three possible pathways of transport of periodontal bacterial DNA from periodontal sites to the synovium:

1. As whole viable cells leading to infection in the joint and reactivation of RA in spite of rheumatic treatment.
2. Via intracellular capture by immune cells, as evidenced by the fact that synovial fluid contains phagocytosed material including IgG, IgM, rheumatoid factor, fibrin, antinuclear factors, immune complexes, and DNA particles.
3. Via free DNA transportation in the bloodstream (39).

A number of different experiments have been carried out to probe these potential pathways. These include inoculation of synovial fluid in different culture media, under aerobic, and anaerobic conditions. As no bacterial growth was detected, these results suggest that there were no viable bacterial cells in the samples studied. Isolated leukocytes from whole blood have also been tested by PCR to detect bacterial DNA and, again, there were no positive samples to any periodontal bacterial species studied suggesting that DNA does not travel from periodontal sites to joints inside immune cells. In the absence of these two possible mechanisms, it would appear that the transport of bacterial DNA is as free DNA (41).

P. gingivalis and rheumatoid arthritis (RA)

P. gingivalis is the main organism associated with chronic PD. It is a gram-negative anaerobic bacteria, the fimbriae of which allow binding of the bacterial cell to host proteins (44).

The IgG and IgA antibody levels against *P. gingivalis*, together with other periodontopathic organisms such as *P. intermedia*, *P. nigrescens*, and *T. forsythia* were higher in serum and synovial fluid from RA patients when compared with controls. The presence of these antibodies could be important in the etiopathogenesis of RA and could represent a potential connection between periodontal and joint diseases (38, 45). On the other hand, it has been reported that the same level of IgG antibody against *P. gingivalis* occurs in serum of patients with a rapidly progressive form of periodontitis, RA, chronic periodontitis, and a control group (34). These authors did not detect differences between RA subjects and the control group, although this could be attributed to the study design and the small sample size involved (34).

As mentioned previously, RA is an autoimmune disease showing a reaction to citrullinated proteins. Citrullination, also termed deamination, is a modification of arginine side chains catalyzed by peptidylarginine deaminase (PAD) enzymes. This posttranslational modification has the potential to alter the structure, antigenicity, and function of proteins. In RA, antibodies to cyclic citrullinated peptides are used in clinical diagnosis. The citrullinated antigens are: fibrinogen, vimentin, collagen type II, and alpha-enolase, all of which are expressed in the joint. Antibodies to citrullinated fibrinogen and collagen type II mediate inflammation by the formation of immune complexes, both in human and animal models, Table 2 (46). *P. gingivalis* produces a microbial enzyme, equivalent to the human PAD enzyme. It has been thought to represent a susceptibility factor for RA. The antigens generated by this enzyme lead the production of rheumatoid factor and local inflammation of both the gingivae and synovium (20). PAD leads to the citrullination of putative RA autoantigen such as fibrin in the synovium, which in association with major histocompatibility complex molecules and antigen-presenting cells, leads to the

Table 2. Association of *Porphyromonas gingivalis* with arthritis in *in vitro* studies

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 gingivalis* *Streptococcus mutans*	Cell culture	Ghosh et al., 2008. (53)
Hyperinflammatory genotype and functional interferences in innate and adaptive immune responses	ELISA	*Porphyromonas gingivalis* *Aggregatibacter actinomycetemcomitans*	Mice	Trombone et al. (31)

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production of anti-CCP antibody (47). In addition, it has been suggested that the immune response to *P. gingivalis* may be involved in breaking immune tolerance to citrullinated antigens (48, 49). As well there are reports of a similarity of sequence and cross-reactivity with bacterial enolase (50).

Some studies have investigated the association between *P. gingivalis* and RA in animal models. One recent study, in which heat-killed *P. gingivalis* was injected into the backs of DA rats, has shown that *P. gingivalis* promotes the development of arthritis as measured by paw swelling (51). This study clearly showed that a pre-existing, extra-synovial chronic inflammatory lesion induced by *P. gingivalis* promotes the development of arthritis in an animal model (51). In another study, *P. gingivalis* and *Aggregatibacter actinomyctemcomitans* were used to induce periodontal disease in a mouse model. It was observed that in a genetically susceptible mouse strain the reaction was associated with higher levels of TNF-α, IL-1β, IL-17, MMP-13, and RANKL, suggesting a shared hyperinflammatory genotype and functional interferences in innate and adaptive immune responses (31).

Another possible mechanism to explain the association between *P. gingivalis* and RA is its effect on cell cycle progression and apoptosis of human articular chondrocytes. Studies have shown that *P. gingivalis* can adhere to and infect primary human chondrocytes affecting cell cycle progression. In this context, *P. gingivalis* might contribute to the tissue damage seen in RA (52). It has also been shown that *P. gingivalis* can cause cell apoptosis and the breakdown of extracellular matrices into macromolecular fragments. Fibronectin fragments are associated with disease severity in both RA and PD but the mechanism is unclear, Table 2 (53).

It has been reported that interleukin-17 (IL-17), a proinflammatory cytokine secreted by the CD4(+) Th17 subset, contributes to bone destruction in RA but, at the same time, it is essential in the host innate immune defense against pathogens such as *P. gingivalis* (54). While recent evidence has shown that Th17 cells are more osteoclastogenic than other T helper subsets such as Th1 or Th2 and ablation of IL-17 signaling prior to the onset of infection with *P. gingivalis* increases susceptibility to periodontal bone loss (55), IL-17RA deficient mice showed enhanced periodontal bone destruction suggesting a bone-protective role for IL-17 (54).

Finally, IgG antibodies to the 40-kD heat shock protein, from *Aggregatibacter actinomycetemcomitans* are significantly higher in RA sera than in the sera of healthy controls (28). Other bacteria such as *Staphylococcus aureus* and *Staphylococcus epidermidis* have also been cited as possible bacterial etiologic agents in late prosthetic infections in RA patients (56, 57). It is also interesting to note that both of these bacterial species can be found in the mouths of some people.

Control of periodontal infection reduces active rheumatoid arthritis (RA)

Recent studies have shown that control of periodontal infection and inflammation by means of scaling, root planing, and oral hygiene in subjects with moderate and severe PD might contribute to a reduction in the signs and symptoms of active RA in terms of a reduction in the serum levels of TNF-α (58). In addition, recent clinical trials have suggested that the treatment of PD might have an important impact on RA severity (58–60).

Dual purpose therapies based on biological links

Tetracyclines, non-steroidal anti-inflammatory drugs (NSAIDs), and biphosphonates (61) have all been used in the treatment of both RA and PD. Tetracyclines are active against gram-negative and gram-positive organisms and have also been shown to inhibit the collagenase activity of MMPs (20). These enzymes are responsible for bone destruction in both diseases and it has been reported that MMPs have an enhanced activity in the synovium of patients with RA (62). Therefore, it follows that tetracyclines may be useful in patients with RA and PD, since they are effective against the putative microorganisms implicated in periodontitis and possibly in RA and also in decreasing bone destruction by inhibiting MMPs (63, 64).

NSAIDs act by inhibiting cycloxygenase, the enzyme responsible for the biosynthesis of prostaglandins. Periodontally diseased tissues have high prostaglandin levels, which are considered to be important mediators of bone resorption in periodontitis (65). NSAIDs are commonly used in the treatment of RA to reduce pain and inflammation. Some NSAIDs can directly inhibit the activation and function of neutrophils (66), and can inhibit TNF-α release from monocytes and natural killer cells (67). These cycloxygenase independent effects may contribute to the efficacy of NSAIDs in the treatment of RA.

Conclusions

There is no question that PD and RA have many pathologic features in common. In the last few decades, periodontal research has provided strong evidence for a correlation between elevated concentrations of serum antibodies against periodontal pathogens and disease severity (34, 45, 68, 69). At the same time, some studies have attempted to identify periodontopathic bacteria in serum and synovial fluid samples from patients with RA using molecular biological assays (39, 41). At the present time however, the detection of microorganisms (viable replicating form) or bacterial DNA in the synovium is not necessarily indicative of an active role in the pathogenesis of RA. While emerging evidence suggests a strong association between the extent and severity of PD in patients affected by RA, this relationship is

unlikely to be causal. Experimental models, especially animal models, need to be established to demonstrate the arthritogenicity of oral microorganisms more definitively.

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Conflict of interest and source of funding statement

There is no conflict of interests in the present study for any of authors.

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