Rheumatoid arthritis is an autoimmune disease caused by periodontal pathogens

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Abstract: A statistically significant association between periodontal disease (PD) and systemic diseases has been identified. Rheumatoid arthritis (RA), which is a chronic inflammatory joint disease, exhibits similar characteristics and pathogenesis to PD. The association between RA and PD has been investigated, and numerous publications on this subject exist. Approximately 20 bacterial species have been identified as periodontal pathogens, and these organisms are linked to various types of PD. The most analyzed species of periodontopathic bacteria are Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, and Aggregatibacter actinomycetemcomitans. Antibodies and DNA from these oral pathogens have been isolated from the sera and synovial fluids of RA patients. This rapid communication describes the role of periodontal pathogens in the etiopathogenesis of RA.

Keywords: etiopathogenesis, chronic arthritis, periodontitis, Porphyromonas gingivalis, systemic disease, animal models, antibiotics

Introduction
Rheumatoid arthritis (RA) is an autoimmune systemic disease that afflicts 0.5%–1% of the population worldwide.1 Periodontitis is characterized by infections that begin with an inflammation of the periodontium and progress to tooth loss.2 Untreated infections may destroy the periodontal ligament and alveolar bone.2 Periodontal disease (PD) is the most chronic infectious disorder, and its prevalence varies between 10%–60% in adults depending on the diagnostic criteria.2 PD includes gingivitis, which is an inflammation of the soft tissue surrounding the teeth, and periodontitis, which occurs with the spread of the disease to the alveolar bone.2

A significant increase in the incidence of PD has been observed in patients with chronic, active RA compared to healthy subjects,3 and the prevalence of RA is higher in PD patients compared to individuals without PD.3

Sulfasalazine was developed in Sweden for the treatment of RA 70 years ago.4 This drug contains a sulphonamide that was the most effective antibiotic of that period and has been proved efficacious in the treatment of RA.4 The mechanism of action of sulfasalazine may include alterations in the intestinal flora because decreased numbers of nonsporing anaerobes are observed in inflammatory bowel disease patients who are treated with sulfasalazine.5

Tetracyclines inhibit most periodontopathic bacteria in vitro and in vivo,6 and minocycline is effective for the treatment of RA and PD.6,7 We have demonstrated previously that clarithromycin and roxithromycin are effective against early and late disease-modifying antirheumatic drug (DMARD)-resistant RA.8–
Roxithromycin and clarithromycin are used clinically in the treatment of anaerobic bacterial infections.\textsuperscript{8–10} The efficacy of these antibiotics is independent of RA severity, and the results are consistent with responses seen in anti-tumor necrosis factor (TNF) treated patients.\textsuperscript{8–10} Levofoxacin is also effective against RA.\textsuperscript{11}

**Periodontal pathogens**

Approximately 20 bacterial species have been identified as periodontal pathogens, and these bacteria are associated with various types of PD.\textsuperscript{12} The most commonly studied periodontopathic bacteria include *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans*.\textsuperscript{12}

*P. gingivalis* is a Gram-negative, asaccharolytic, anaerobic, nonmotile, nonsporing, short-rod microorganism that grows in brown- or black-pigmented colonies on blood agar.\textsuperscript{12} Some species that produce PD are abundant in the oral cavity and the upper gastrointestinal system, respiratory tract, and colon.\textsuperscript{12} *P. gingivalis* possesses the highest proteolytic activity of the Gram-negative bacteria that have been isolated from PD-affected areas, and this species exhibits the highest virulence pattern in inoculated animals in a simple pathogenicity test.\textsuperscript{12} *P. gingivalis* produces arginine-specific (gingipain R) and lysine-specific (gingipain K) cysteine endopeptidases.\textsuperscript{12} Various virulence factors, such as polysaccharide capsule, fimbriae, opsonin (gingipain K) cysteine endopeptidases.\textsuperscript{13} Various virulence factors, such as polysaccharide capsule, fimbriae, opsonin (gingipain K) cysteine endopeptidases.\textsuperscript{13} Various virulence factors, such as polysaccharide capsule, fimbriae, opsonin (gingipain K) cysteine endopeptidases.\textsuperscript{13}

**Genetics of rheumatoid arthritis**

The strongest genetic association in RA is observed with the major histocompatibility complex class II, DRβ1 (human leukocyte antigen [HLA]–DRβ1) gene. This highly polymorphic gene encodes a cell surface molecule that is primarily expressed in antigen-presenting cells, such as dendritic cells, macrophages, and B cells. This molecule mediates the presentation of peptide antigens to T cells, which stimulates the cellular response to these antigens. Many variants of HLA–DRβ1 are associated with RA, and some variants are also associated with periodontitis.\textsuperscript{13} This association is due to five key amino acids on the side wall of the HLA–DRβ1 molecule (QK[RG]RAA). This sequence is a shared epitope, and predisposition to the disease requires the presence of positively charged arginine and lysine residues at position 71 in the HLA–DRβ1 molecule. This positively charged motif sequence presents citrulline residue-containing peptides to T cells.\textsuperscript{13}

In August 2001, Ogrendik et al hypothesized that *P. gingivalis* is an environmental factor that impairs tolerance against autoantigens that contain citrulline in a genetically susceptible host.\textsuperscript{13} *P. gingivalis* is responsible for the severe forms of PD.\textsuperscript{13} This bacterium produces peptidyl arginine deiminase (PAD)\textsuperscript{12} and can citrullinate the terminal arginine residues of peptides.\textsuperscript{13} Therefore, the chronic presence of these bacteria in inflamed periodontal tissue may induce the local production of citrullinated peptides. The microenvironment in chronic inflammatory oral lesions may be rich in proinflammatory cytokines, such as TNF–α and IL-1β, which facilitates the presentation of citrullinated antigens to T cells by local antigen-presenting cells. The immune response in this environment shifts to homolog citrullinated human autoantigens, due to the molecular similarity and evolution. The ubiquitous enzyme enolase is a candidate antigen because a citrullinated form of enolase has been identified as an autoantigen in RA.\textsuperscript{14} The incubation of wild type *P. gingivalis* with fibrinogen or α-enolase destroys these proteins and the citrullination of the carboxyl-terminal arginine residues.\textsuperscript{15} *P. gingivalis* titration in RA patients is correlated with the concentration of anticitrullinated protein/peptide antibodies.\textsuperscript{16}

**Etiology of rheumatoid arthritis**

We observed higher serum levels of antibodies against disease-causing periodontal bacteria in RA patients compared to a control group in a case-control study\textsuperscript{13} and reported that anti-*P. gingivalis* antibodies were more frequently observed in RA patients than healthy controls. Furthermore, the concentrations of autoantibodies that are related to RA and C-reactive protein are also higher in people with *P. gingivalis* infections. This study was conducted from August 2001 to August 2002 in Turkey and Australia.\textsuperscript{13} Similar results have been demonstrated in other case-control studies.\textsuperscript{17}

However, the detection of bacterial DNA, rather than antibodies, in the synovial fluid of RA patients is a more significant result because it indicates the transfer of bacterial DNA from the infection site into the joints. Recent studies have focused on the determination of bacterial DNA in the joints of RA patients, using checkerboard DNA–DNA hybridization or polymerase chain reaction (PCR) detections.\textsuperscript{18,19} *P. gingivalis*, *T. forsythia*, and *P. intermedia* bacteria have been determined in synovial fluid samples from patients with RA and psoriatic arthritis through the detection of checkerboard
DNA–DNA hybridization. A recent cross-sectional study of 19 patients with periodontitis and resistant RA who received intensive therapy with DMARDs (eg, methotrexate, sulfasalazine, leflunomide, and chloroquine) demonstrated the presence of *P. intermedia* (89.4%), *P. gingivalis* (57.8%), and *Prevotella nigrescens* (21.0%) using PCR. These two studies clearly support the presence of the chromosomal DNA of PD-associated bacteria in the sera and synovial fluid of RA patients. Synovial inflammation in RA facilitates the detection of oral bacterial DNA.

PD patients frequently experience bacteremic episodes. The frequency of bacteraemia is 13% after ultrasonic measurements; 20% after periodontal interventions; and 3% after tooth brushing. Periodontal pathogens can directly access the blood circulation, and periodontal bacterial DNA is transported from the periodontal regions to the synovium in the form of free DNA.

**Animal models**

The association between *P. gingivalis* and RA has been investigated in animal models. The injection of heat-killed *P. gingivalis* into the backs of rats with RA stimulates arthritis development as measured by paw swelling. This same group examined preexisting PD and its effects on arthritis using a RA rat model. PD was precipitated using an oral gavage with *P. gingivalis*, and arthritis was initiated using the collagen antibody-induced arthritis model. The PD rats exhibited higher inflammation levels and more radiographic joint damage following arthritis compared to rats without PD. This study demonstrated that *P. gingivalis*-induced preexisting PD enhanced the formation and severity of arthritis. These results demonstrate that PD caused by bacterial infection increases inflammation in distant synovial tissues.

In another investigation, DR4 transgenic rats were immunized with enolase that was isolated from *P. gingivalis* to specify the relationship between RA characterized by anticitrullinated enolase peptide (anti-CEP) antibody positivity and *P. gingivalis*. The anti-CEP antibody is specific to RA, and it is largely associated with alleles that contain the *HLA–DRB1* shared epitope. This study demonstrated a more severe arthritis in the rats immunized with enolase (native and citrullinated forms) isolated from both humans and bacteria compared to the control group. Furthermore, immunization with *P. gingivalis* enolase generated autoimmunity to human alpha-enolase and promoted the progression of arthritis. These results suggest that enolase from *P. gingivalis* in its most native form precipitates the onset of RA in some patients.

**Conclusion**

Gram-negative anaerobic bacilli may cause infections anywhere in the body; the most common types are oral and dental, pleuropulmonary, intra-abdominal, female genital tract and skin, soft tissue and bone infections. In other words, it does not mean that the individuals with RA should have periodontitis also. Therefore, the above results indicate that periodontopathic bacteria are responsible for the etiopathogenesis of RA in a genetically susceptible host. These results will guide more comprehensive and efficacious treatment strategies for RA.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**