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Periodontal disease and rheumatoid arthritis: the evidence accumulates for complex pathobiologic interactions

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Abstract

Purpose of review—This review was conducted to focus on the recent clinical and translational research related to the associations between periodontal disease and rheumatoid arthritis.

Recent findings—There is a growing interest in the associations between oral health and autoimmune and inflammatory diseases. A number of epidemiologic studies have described associations between rheumatoid arthritis and periodontal disease. Recent clinical studies continue to support these reports, and are increasingly linked with biological assessments to better understand the nature of these relationships. A number of recent studies have evaluated the periopathogenic roles of *Porphyromonas gingivalis*, the oral microbiome, and mechanisms of site-specific and substrate-specific citrullination. These are helping to further elucidate the interactions between these two inflammatory disease processes.

Summary—Studies of clinical oral health parameters, the gingival microenvironment, autoantibodies and biomarkers, and rheumatoid arthritis disease activity measures are providing a better understanding of the potential mechanisms responsible for rheumatoid arthritis and periodontal disease associations. The cumulative results and ongoing studies have the promise to identify novel mechanisms and interventional strategies to improve patient outcomes for both conditions.

Keywords

citrullination; periodontal disease; periodontitis; *Porphyromonas gingivalis*; rheumatoid arthritis

INTRODUCTION

In the past few years, increasing attention has been given to aspects of oral health in patients with rheumatoid arthritis, especially related to associations with periodontal disease. The numbers of publications are on the rise, driven in part by interest in the role of citrullination

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Conflicts of interest

There are no conflicts of interest.

and attendant autoantibody responses as a disease-defining feature of rheumatoid arthritis, and the recognition that oral bacteria and inflammation may play important roles.

Observations related to oral conditions and inflammatory arthritis extend back for centuries, with Hippocrates suggesting that pulling teeth could cure arthritis. Common oral manifestations in rheumatoid arthritis include Sjogren's syndrome and temporomandibular joint disease (TMD), and studies have suggested associations with periodontal disease in patients with rheumatoid arthritis. Although a number of hypothesized interactions between the diseases were proposed, cross-sectional association studies could not discern temporal relationships. Initial conceptualizations for the nature of the relationship involved shared inflammatory disease pathways, shared risk factors such as smoking, oral hygiene difficulties from TMD and/or peripheral joint dysfunction, effects of nonsteroidal antiinflammatory drugs, steroids, and immunosuppressants, and xerostomia from Sjogren's.

As the importance of peptide citrullination as an etiopathologic event in rheumatoid arthritis has been elucidated, studies have focused on the expression and function of the peptidylarginine deiminase (PAD) enzymes that can lead to posttranslational modification, neoepitope generation, with subsequent development of anticitrullinated peptide antibodies (ACPA). A seminal discovery that a major bacterial species involved in the development and propagation of periodontal disease, *Porphyromonas gingivalis (Pg),* has a PAD capable of citrullination [1] fuelled interest and additional investigation of citrullination as a mechanistic link between the two conditions. Moreover, additional studies of the periodontal microenvironment and immunological mechanisms in periodontal disease have provided additional insights.

This review focuses on recently published studies that are adding to the knowledge base and broadening understanding of clinical and biological links between rheumatoid arthritis and periodontal disease, with references to major historical studies and topical reviews.

ORAL HEALTH IN RHEUMATOID ARTHRITIS

A number of oral manifestations have been described in rheumatoid arthritis patients. These include the well recognized association with Sjogren's and xerostomia, TMD [2■], methotrexate-induced ulcers, and an increasing emphasis on periodontal disease [3]. Oral mucosal involvement in autoimmune diseases, including rheumatoid arthritis, occurs with high frequency [4■]. Symptomatic xerostomia and secondary Sjogren's are not uncommon in rheumatoid arthritis patients, with recent studies [5■,6■] providing prevalence estimates of between 3 and 30%, depending on the definition. Recently published classification criteria for primary Sjogren's syndrome by the American College of Rheumatology and the Sjogren's International Collaborative Clinical Alliance Cohort [7■■] will facilitate more accurate descriptions of Sjogren's prevalence, a condition with considerable impact on overall healthrelated quality of life [8■,9■]. Whether secondary Sjogren's in rheumatoid arthritis is associated with an increased periodontal disease remains unclear; some studies [10–12] have suggested increased periodontal disease and gingivitis in Sjogren's, but others have not.

CLINICAL FEATURES AND PREVALENCE OF PERIODONTAL DISEASE

Periodontal disease or periodontitis affects the tissues that surround and secure the teeth, including the gums or gingiva, the ligaments providing support, and the bone into which the tooth is anchored [13■■]. Periodontal disease is characterized by the progression beyond an initial stage of gingivitis, to a chronic inflammatory process that begins to affect connective tissues surrounding the tooth leading to attachment loss; in the absence of proper treatment, periodontal disease may progress to bone destruction and tooth loss. Clinical characteristics of periodontal disease include bleeding and friable gums, gingival recession, deepening pockets surrounding the tooth (indicating loss of anchoring attachments), and eventual tooth loosening. Periodontal disease has a considerable impact on oral health-related quality of life [14■■]. Risk factors associated with periodontal disease include smoking, age, dental hygiene, minority status, and socioeconomic status. A recent review summarized the global prevalence estimates of periodontal disease from various populations [15■■]. The National Health and Nutrition Examination Survey (NHANES) assessment in 2009–2010 conducted a full mouth examination at six sites per tooth and showed the overall rate of periodontal disease in the general US population over age 30 is 47.2%, 30% moderate and 8.5% severe [16■■]. These estimates were markedly increased compared with prior NHANES-III reports, in which only a partial mouth examination was performed. Several reports have emphasized that the method of oral examination, numbers of sites evaluated, and periodontal disease case definitions considerably influence prevalence estimates [16■■,17■,18].

ASSOCIATION STUDIES BETWEEN PERIODONTAL DISEASE AND RHEUMATOID ARTHRITIS

A number of large epidemiological studies [19■■, 20■■,21] and smaller case–control and cohort studies have been published showing associations between rheumatoid arthritis and periodontal disease, and have been extensively reviewed. Most have reported positive associations with periodontal disease, comparing rheumatoid arthritis patients with controls. Periodontal parameters have not been uniformly reported, nor have newer periodontal disease case definitions been applied. Studies that used patient report data [22] or included partial dental examinations (e.g. NHANES-I and NHANES-III) with reported associations between certain periodontal parameters and rheumatoid arthritis [3,23■] may have underestimated periodontal disease prevalence [17■,18]. A recent report in Taiwanese rheumatoid arthritis patients confirmed earlier association studies [24■]. Even with their limitations, including their cross-sectional nature, variability in the dental endpoints reported, periodontal disease case definitions, extent of oral exams, limited information on rheumatoid arthritis disease characteristics or analysis of confounders, including steroid, and immunomodulatory drug use, the existing studies provide an overwhelming body of evidence to demonstrate that periodontal parameters including bleeding, gingivitis, and depth of tooth pockets are worse in rheumatoid arthritis patients [25]. An important confounder that has been variably reported is smoking status. Although smoking is a well recognized shared risk for rheumatoid arthritis and periodontal disease, Potikuri *et al.* [26■■] recently reported that the associations are present in nonsmoking rheumatoid arthritis patients.

Some studies [27,28] have reported that periodontal disease severity tracks with rheumatoid arthritis disease activity. Other studies [29–32] have suggested that nonsurgical periodontal therapy improves rheumatoid arthritis parameters, including a recent study showing reductions in erythrocyte sedimentation rate/C-reactive protein, tumor necrosis factor (TNF) levels, and Disease Activity Score. Though not designed to address a periodontal hypothesis, a rheumatoid arthritis treatment study [33] with doxycycline with methotrexate (MTX) showed that 20 mg/day doxycycline (the dose typically used to treat periodontal disease) had similar ACR50 responses as a 100-mg dose; both doses were superior to placebo–MTX. The net effects of TNF inhibition on periodontal disease parameters remain an open question but are of interest given the increased TNF levels in gingival crevicular fluid and inflamed periodontium. A recent small study [34■] suggested that rheumatoid arthritis patients with periodontal disease had less improvement in rheumatoid arthritis disease activity with TNF inhibitors; others [30,35,36] have reported that rheumatoid arthritis patients treated with TNF inhibitors had improvement in some, but not all, periodontal disease parameters. Clinical studies [37] have also shown that alveolar bone loss in rheumatoid arthritis patients with periodontal disease parallels rheumatoid arthritis erosions at other sites.

MOVING FROM CLINICAL ASSOCIATIONS TO MECHANISM

Rheumatoid arthritis and periodontal disease share a number of pathobiologic processes that have been previously reviewed [21,38■■,39,40■,41–43, 44■]. These include similar cellular participation at the inflammatory focus, microenvironmental and serum cytokine, matrix metalloproteinase and other mediator profiles, and osteoclast-mediated bone destruction. Studies [45] have shown the presence of periopathogenic bacteria in the synovium of patients with rheumatoid arthritis indicating that joint seeding and localized inflammatory amplification may be operative. Others [46,47] have shown common genetic risk factors including the Human Leukocyte Antigen (HLA)-DR shared epitope and polymorphisms and epigenetic modifications in cytokine genes, including a recent report showing similar interleukin-6 promoter methylation in rheumatoid arthritis and periodontal disease [48■].

A foundational event in the establishment of periodontal disease is the orderly development of a biofilm composed of an array of oral bacteria. In the initial colonization stages, a localized inflammatory response may be seen, but not tissue destruction. The later colonization with a group of specific bacteria appears to be necessary for progression. This group of predominantly anaerobic bacteria, recently referred to as ‘keystone pathogens’, have unique properties promoting their survival through a number of virulence factors, mechanisms for host defense evasion, tissue penetration, and activation of inflammatory and tissue destructive pathways [49■■]. As recently reviewed, modern methods of bacterial identification and taxonomic classification are providing a growing appreciation for the complex interactions between bacterial species and their combinatorial interactions with host defenses [50■■].

PORPHYROMONAS GINGIVALIS

The gram-negative, anaerobic, oral coccobacillus *Pg* has received considerable attention for its role in the development of periodontal disease. This bacterial species is rarely present in

periodontally healthy individuals, but colonization by *Pg* is one of the permissive steps in the propagation of the periodontal lesion. *Pg* has a number of characteristics that allow it to initially elude host defense mechanisms, promoting tissue ingress, with a resultant upregulation of a number of local inflammatory responses, further propagating tissue damage. The virulence factors and properties of *Pg* have been recently comprehensively reviewed [38■■,51■■,52]. These include the gingipain family of arginine-specific and lysine-specific proteases [53], lipopolysaccharide, and fimbriae that have a number of deleterious effects on tissue. Among its features, *Pg* traverses the normally tight epithelial junctions through specific interactions with integrins and the cleavage of adhesion molecules, inactivates certain proinflammatory cytokines and chemokines, degrades components of the extracellular matrix, increases oxidative stress, can cause cell apoptosis including chondrocytes [54■], and can activate coagulation pathways by cleaving fibrinogen and induce vascular permeability via the kinin cascade [55].

The recognition that *Pg* was unique among oral bacteria in having a PAD spurred considerable interest among the rheumatologic community, given the appreciation of ACPA in rheumatoid arthritis. This provided an additional potential mechanistic explanation for the relationship between periodontal disease and rheumatoid arthritis, a hypothesis that has been reviewed in depth by others [21,38■■,41, 42,56■,57].

CLINICAL STUDIES OF *P. GINGIVALIS* IN RHEUMATOID ARTHRITIS

A number of studies [26■■,58,59■,60■] have evaluated whether exposure to *Pg* is seen in rheumatoid arthritis and whether exposure is associated with rheumatoid arthritis autoantibodies. Using an antibody against *Pg*, Mikuls *et al.* [58] demonstrated that anti*Pg* presence and titers were higher in rheumatoid arthritis than controls. They also showed that *Pg* titers were associated with anticyclic citrullinated protein (anti-CCP) antibodies of the IgM and IgG_2 isotypes. Recent studies have also studied relationships between anti-*Pg* and rheumatoid arthritis antibodies, though in a recent study [59■] of Japanese rheumatoid arthritis patients, anti-*Pg* was associated with rheumatoid factors, but not with anti-CCP. In another study [60■] that examined 11 periodontal pathogens in subgingival plaque profile from rheumatoid arthritis patients, there was no association of the presence or abundance of *Pg* with rheumatoid factors, but ACPA results were not reported, and rheumatoid factor seropositivity in the population was very low. And in another study [61■], antibodies to *Pg* were associated with worse periodontal disease parameters in rheumatoid arthritis patients but not with five different specific ACPA from enolase, fibrinogen, and vimentin.

Two recent studies have further examined relationships between *Pg* exposure and rheumatoid arthritis antibodies in two important populations. The first of these examined ACPA and antibodies against three different periodontopathic bacteria, including *Pg*, in individuals at risk for developing rheumatoid arthritis (HLA-DR4 and/or being a firstdegree relative of a person with rheumatoid arthritis) [62■■]. Similarly to earlier reports in another high-risk cohort of native Americans [63], they showed anti-*Pg* as a marker of potential periodontal disease was associated with ACPA and rheumatoid factors. In the recent study, this relationship was seen with anti-*Pg* but not with the other oral bacteria tested, suggesting

that *Pg* exposure was permissive in the development of rheumatoid arthritis antibodies, even before the presence of any clinical arthritis.

The second study by Scher *et al.* [64■■] examined anti-*Pg* and added sophisticated multiplex pyrosequencing to evaluate the oral microbiome in groups of individuals with early rheumatoid arthritis, established rheumatoid arthritis, and healthy adults. Prior studies had been cross-sectional but had not addressed associations at the inception of rheumatoid arthritis. These investigators showed that periodontal disease was present and frequently severe in the early and established rheumatoid arthritis groups, more than that in controls (62%, 52%, 22% with severe periodontal disease, respectively). In contrast to other reports, neither anti-*Pg* nor the abundance of *Pg* organisms was higher in rheumatoid arthritis patients compared with controls, nor was there a relationship between anti-*Pg* or *Pg* abundance and the presence of rheumatoid arthritis autoantibodies; however, they identified additional bacterial species apart from *Pg* that were associated with rheumatoid arthritis autoantibodies (*Anaeroglobus geminatus*) and new-onset rheumatoid arthritis (*Prevotella* and *Leptrotrichia* species).

ROLES OF *P. GINGIVALIS* IN CITRULLINATION

A number of studies [1,65] have been reported since the initial identification of *Pg*-PAD to evaluate its function and potential roles in citrullination. To date, no other prokaryotes have been identified to have a PAD, though five human enzymes are expressed [66,67]. In common with other PADs, *Pg*-PAD is susceptible to autocitrullination [65]. Although human PAD autocitrullination may have functional consequences [68], the effect in *Pg*-PAD is unknown. The associations of anti-*Pg* and ACPA need to be reexamined; it is possible that anti-*Pg* assays were detecting bacterial ACPA as a reason for the concordance. Determining the properties of different PADs in terms of substrate specificity has been an area of active research [69■], as it is now thought that specific citrullinated peptides are tightly coupled with specific shared epitope alleles [67,70,71]. That human α-enolase, a putative rheumatoid arthritis autoantigen [72], had high homology with enolase found in *Pg*, and that an immunodominant peptide susceptible to citrullination [citrullinated enolase peptide-1 (CEP-1)] was identical and recognized by rheumatoid arthritis sera were important observations implicating *Pg* with rheumatoid arthritis autoantigen generation [73]. Through a series of experiments with PAD-deficient and gingipaindeficient strains of *Pg*, Wegner *et al.* [74] demonstrated that *Pg* could citrullinate its own proteins, but was dependent on the activity of its argininespecific gingipain exposing carboxy-terminus residues for *Pg*-PAD activity. These studies [67,70,75] contributed further evidence toward a mechanistic explanation for how *Pg*, through the cooperative interactions of its gingipains and PAD, could potentially initiate early citrullination, thus providing an initial break of tolerance in ACPA development and further epitope spreading. A recent report described an additional function of *Pg*-PAD on tissue invasion in periodontal disease through direct inhibition of epidermal growth-factor via citrullination, an activity not seen with human PAD-2 or PAD-4 [76■].

The expression of PADs in target tissues has been studied, but only recently examined in oral tissue. A recent study [77■■] demonstrated that citrullination is more abundant in

inflammatory periodontitis than in noninflamed tissue, and localized to fibroblasts, endothelial cells, and infiltrating inflammatory cells. The study also reported increased expression of PAD-2 and PAD-4, associated with increasing inflammation. Of note, PAD-2 expression is upregulated with smoking, a risk for periodontal disease [78]. Another recent study [79■■] confirmed increased citrullination in inflammatory periodontal stroma but also expression in buccal epithelium of periodontitis and controls. There have been no reports of *Pg*-PAD expression in tissues or cells to date.

ANIMAL STUDIES OF PERIODONTAL DISEASE AND ARTHRITIS

A number of animal studies have been conducted to evaluate interactions between periodontal disease and arthritis. In an adjuvant arthritis model, killed *Pg* organisms within sponges were implanted under the back skin of rats [80]; arthritis was induced using varying adjuvant doses. The threshold for arthritis induction was lower in animals with *Pg* exposure, suggesting a priming effect of *Pg* that augmented arthritis development. Although previous rat adjuvant arthritis studies reported periodontal bone loss with arthritis suggesting reciprocal interactions [81], this was not seen in the recent report. In studies [82■,83■] using a mouse antigen-induced arthritis (AIA) model, mice with bacterially-induced periodontitis were compared with those without, and groups were treated with anti-TNF therapy and/or antimicrobials. Several findings were reported: first, early bone loss around teeth was seen in AIA mice without bacterial exposure at a severity similar to that with direct bacterial installation; second, clearing oral bacteria with antiseptic prevented periodontal bone loss, but had no effect on arthritis; third, the presence of AIA exacerbated bacterially induced periodontal disease; finally, both arthritis and alveolar bone loss were reduced in the presence of anti-TNF therapy. Another important observation was that a non-*Pg* species of oral bacteria, *Aggregatibacter actinomycetemcomitans*, could worsen arthritis. Another group recently reported that, in the type II collagen-induced arthritis (CIA) model, mice with prior periodontal disease induction from oral *Pg* installation had more severe arthritis, based on inflammation and bony changes [84■]. Moreover, they demonstrated that mice with *Pg*-induced periodontal disease, but without CIA, had bony destruction in peripheral joints, without concomitant inflammation. In another recent CIA study [85■], alveolar bone destruction was worsened in CIA mice compared with controls, mediated through both increased osteoclast activity and a reduced osteoblastic bone formation.

Based on their earlier reports that *Pg* enolase was homologous to human enolase, and susceptible to CEP-1 citrullination [73,74], Kinloch *et al.* [86■] recently tested whether *Pg*-derived peptides could participate in the generation of rheumatoid arthritis-related, HLA-DR4-restricted autoantigen responses and arthritis development. Using the DR4-IE-transgenic mouse arthritis model [87], animals were immunized using *Pg*-enolase and human α-enolase, in both native and citrullinated forms. Interestingly, rapid arthritis induction was seen with both enolase forms, with either bacterial or human protein. Animals immunized with *Pg*-enolase also generated antibodies that recognized human enolase. Although not showing that citrullinated enolases were more reactive in the DR4-restricted model, the study demonstrated that a *Pg* protein could induce arthritis and propagate an immune response against citrullinated peptides. Another group conducted a similar series of experiments using citrullinated and noncitrullinated forms of human enolase in several

arthritissusceptible mouse strains [88■]. Although antibodies developed against both forms, arthritis did not develop, clinically or histologically, in any of their experiments. The reasons for the discordant findings between the two groups are unclear, but merit additional exploration.

DISCUSSION

Research in the area of periodontal disease and rheumatoid arthritis in the last 2 years has confirmed long-standing observed associations between the two disease processes. New observations have demonstrated that periodontal disease is present, and severe, early in the rheumatoid arthritis disease process providing further evidence toward a causal or permissive event. Studies from cohorts at high risk for rheumatoid arthritis have provided additional evidence of periodontal bacterial exposure in the prerheumatoid arthritis state and evidence for differential bacterial colonization in those with early rheumatoid arthritis, including species beyond *P. gingivalis*. Recent animal studies support bidirectional relationships between periodontal bacteria, inflammation, periodontal bone destruction, and joint disease, mediated at least in part through TNF.

There is growing interest in better understanding of citrullination in periodontal disease, and the function of *Pg*-PAD in this process. Although *Pg*-PAD can citrullinate its own proteins that cross-react with human citrullinated peptide homologues, in the case of enolase, it is unclear whether citrullination is necessary for arthritis induction. The descriptions of ubiquitous citrullination in normal oral mucosa, and its increase in periodontal disease with concomitantly expressed PAD-2 and PAD-4, demonstrate the likely participation of microenvironmental inflammation in citrullinating events. Moreover, protein citrullination may have other functional and regulatory consequences through activation and inactivation of proteins.

The growing appreciation for oral bacteria interactions and their effects alone and in concert emphasizes the complex interplay among different species in amplifying local inflammatory and immunoregulatory pathways. Although the unique contribution to periodontal disease propagation by *Pg* as a single species may be considerable, the likelihood for considerable redundancies of function with other bacteria seems likely. In light of emerging research, the initial emphasis on *Pg* as a single bacterial species to explain the associations between periodontal disease and rheumatoid arthritis may be inadequate to explain the multiple intersecting pathobiologic pathways in these diseases.

As is evident from the studies that continue to emerge, collaborations among immunologists, oral pathologists, microbiologists, periodontists, rheumatologists, and systems biologists are increasingly needed to fully understand the relationships between rheumatoid arthritis and periodontal disease. The area is ripe for further clinical and translational research, grounded in studies in which the oral and rheumatologic conditions are clinically well characterized using uniform outcome measures, as well as biomarker analyses from different relevant sites. Complementary basic research is needed to dissect the complex biochemistry, immunology, molecular, and cell biology that provide the mechanistic underpinnings.

Based on the present research, a number of clinical questions have been posed: Will treatment of clinical or subclinical periodontal disease in individuals at risk for rheumatoid arthritis succeed in preventing rheumatoid arthritis development? Will specific treatment of periodontal disease lead to improvement in rheumatoid arthritis parameters? These questions begin to raise logistical and ethical issues: How large and how long must a study be to demonstrate primary prevention? Can a secondary treatment study be done in isolation, or should it be done as an adjunct to other DMARDs? What would be the expected magnitude of response? If prevalent periodontal disease is identified, can that patient be randomized to receive suboptimal or no treatment for the dental condition, with tooth loss a known outcome of treatment delay? Although some have proposed that eradication or immunization against *Pg* could improve the periodontal condition, and thus reduce arthritis, will this be adequate to prevent or sufficiently decrease localized oral inflammation? And although a strategy of inhibiting *Pg*-PAD may be attractive, the redundancies in function of individual PAD enzymes and their substrates raise questions related to specificity.

CONCLUSION

The research reviewed highlights recent studies describing the relationships between rheumatoid arthritis and periodontal disease, and the potential biological mechanisms to explain these associations. The increased focus is resulting in a deeper appreciation of the oral manifestations of rheumatoid arthritis. As a consequence, dental assessment and attention to oral hygiene assume an increasingly important part of the clinical management of the rheumatoid arthritis patient. An increasing number of mechanistic studies are being reported that are likely to reveal additional interactions between these related diseases, and to provide insights for treatment and prevention. Closer attention to oral health in all patients will improve quality of life and address what is now recognized as an important rheumatoid arthritis comorbidity.

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KEY POINTS

- Periodontal disease is common, often severe, and present at all stages of rheumatoid arthritis, including early disease.
- The inflammatory periodontal microenvironment may play a role in the development of rheumatoid arthritis, or augment systemic inflammation and immune responses in disease propagation.
- Specific strains of oral bacteria, including *P. gingivalis*, and localized inflammatory responses may result in citrullination events that serve to break immunological tolerance.
- Recent studies highlight the complex interactions between the oral microbiome and host defense and immunological mechanisms, and the importance of a multidisciplinary approach to evaluation.