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Review

Rheumatoid arthritis and periodontal disease

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ABSTRACT

The prevalence of periodontal disease has increased two-fold among patients with rheumatoid arthritis (RA) compared to the general population. This increased prevalence is unrelated to secondary Sjögren's syndrome but instead reflects shared pathogenic mechanisms, including an increased prevalence of the shared epitope HLA-DRB1-04; exacerbated T-cell responsiveness with high tissue levels of IL-17; exaggerated B-cell responses, with plasma cells being the predominant cell type found within gingival tissue affected with periodontitis and B cells being twice as numerous as T cells; RANK overexpression; and an increase in the ratio of RANK-L over osteoprotegerin with a high level of RANK-L expression on gingival B cells, most notably those capable of recognizing *Porphyromonas gingivalis*. Other factors conducive to periodontitis include smoking and infection with the Epstein-Barr virus or cytomegalovirus, which act by promoting the growth of organisms such as *P. gingivalis*, whose DNA is often found in synovial tissue from RA patients. *P. gingivalis* produces the enzyme peptidylarginine deiminase that induces citrullination of various autoantigens, and levels of anti-CCP antibodies are considerably higher in RA patients with than without periodontal disease, suggesting that periodontitis may contribute to the pathogenesis of RA. Further support for this hypothesis comes from evidence that other antigens involved in RA, such as Hc-gp39, are also present in gingival tissue. TNF α antagonists slow alveolar resorption but may perpetuate infection of periodontal pockets. Therefore, rheumatology patients, including those taking biotherapies, are likely to benefit from increased referral to dental care (e.g., scaling, root planing and, if needed, dental surgery), particularly as periodontitis is also associated with an increased risk of premature atheroma.

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1. Rheumatologists should pay closer attention to the gums of their patients with rheumatoid arthritis

Rheumatologists rarely examine the oral cavity of patients with rheumatoid arthritis (RA). Nevertheless, RA patients are at increased risk for periodontal disease, which develops earlier and is more severe than in the general population [1]. In addition, the last few years have brought disturbing evidence of pathogenic similarities between RA and periodontal disease. Thus, organisms such as *Porphyromonas gingivalis* may play a role in both conditions [2], and similar bone resorption mechanisms may underlie the joint erosions seen in RA and the tooth loss characteristic of periodontitis.

Some degree of periodontitis is found in 75% of adults. Furthermore, evidence of periodontitis is detectable in two-thirds of adolescents, a population characterized by heavy consumption of soft drinks, which promote the growth of the 200 or so bacterial species involved in dental plaque formation. These data indicate a need for frequently referring rheumatology patients to dental care

to ensure that appropriate interventions are carried out (scaling, root planing and, if needed, dental surgery).

2. Natural history of periodontitis

The periodontium is composed of the specialized tissues that maintain the tooth in the socket, namely the gingiva, periodontal ligament, and cementum (to which the ligament attaches). Chronic gingival inflammation gradually destroys the periodontium, leading to tooth loss. The first sign is bleeding, which may occur only when a probe is used to measure the depth of the periodontal pockets. A pocket depth of 5 mm or more (stage II) indicates separation of the gingiva from the tooth, which allows penetration into the pocket of dental plaque, scale, food and, more importantly, oral bacteria, all of which exacerbate the inflammation (Fig. 1). The gums swell, recede from the teeth, and bleed readily upon contact. Exposure of the root surface leads to pain in response to heat or cold, as the dentine at the neck of the tooth is highly sensitive. The alveolar bone begins to undergo resorption. Stage III periodontal disease is defined as pocket depth greater than 6 mm. At this stage, bone resorption often leads to detachment of the periodontal ligament followed by abnormal tooth mobility and, eventually, tooth loss.

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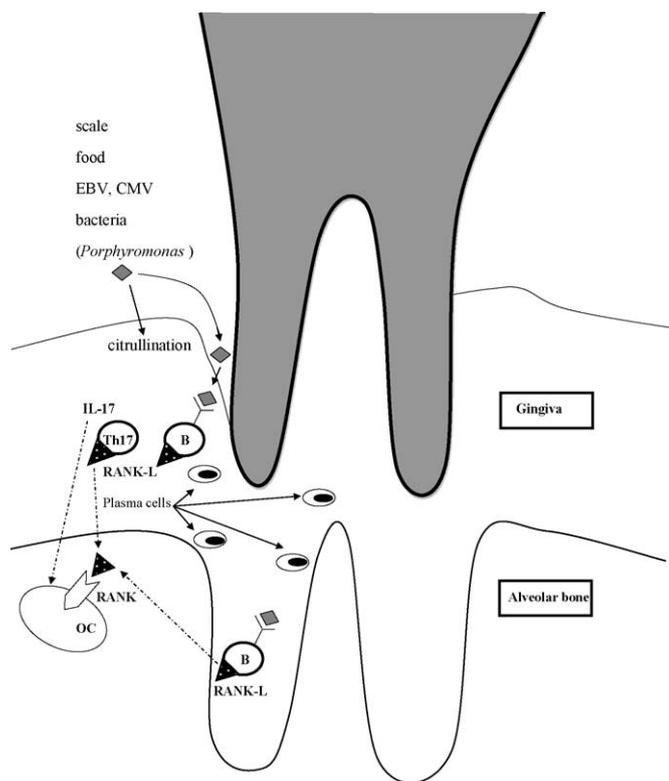


Fig. 1. Food and scale deposit on the neck of the tooth, initiating an inflammatory response. Then, smoking and infection with the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) promote the growth of bacteria such as *Porphyromonas gingivalis*, which can penetrate within the gingival mucosa, leading to the following events: (a) citrullination of some proteins, which may promote loss of tolerance to citrullinated self-antigens in predisposed individuals, most notably during RA; and (b) an immune response, with marked involvement of B cells, which are twice as numerous as T cells (including Th-17 cells that produce IL-17, thereby promoting osteoclastogenesis). B cells specific of some organisms such as *P. gingivalis* probably make a larger contribution than T cells to osteoclast proliferation, most notably via the release of RANK-L. The result is gradual resorption of alveolar bone and eventually loss of teeth via a mechanism similar to that responsible for subchondral bone erosions in RA.

3. Increased prevalence and severity of periodontal disease in rheumatoid arthritis, independently from the presence of sicca syndrome

Studies consistently showed that the prevalence of periodontal disease was increased (about two-fold on average) in patients with RA [1,3,4]. Furthermore, disease severity was greater in RA patients [5]. The largest study evaluated 4461 individuals aged 60 years or older, among whom 103 had RA [6]. After adjusting on age, sex, and smoking status, patients in the RA group had about two-fold increases in edentulism (odds ratio [OR], 2.27; 95% confidence interval [95%CI], 1.56–3.31) and periodontitis (OR, 1.82; 95%CI, 1.04–3.20), and the risks of these events were highest in the RA patients with rheumatoid factors [6]. Another study showed that the periodontitis score in RA patients correlated with the erythrocyte sedimentation rate, C-reactive protein level, swollen joint count, and Health Assessment Questionnaire score [7]. Periodontitis is associated with HLA-DRB1-04 in patients with [8] and without [9] RA. In RA patients, joint destruction at the wrists is associated with alveolar resorption ($P < 0.001$), and bone destruction at both sites is associated with the shared epitope (OR, 2.5) [8] (box).

Patients with sicca syndrome exhibit increased cavity formation and high rates of oral lactobacilli and yeast carriage. However, neither the increased prevalence nor the increased severity of periodontal disease in RA is ascribable to sec-

Box 1: Links between periodontitis and rheumatoid arthritis.

- Periodontitis is twice as common and twice as severe in patients with than without RA, and RA patients are twice as likely to become edentulous [6].

- The clinical and radiological severity of periodontitis correlate with those of RA [7,8].

- Risk factors for both conditions are HLA-DRB1-04 [8,9], smoking [40], and infections with the Epstein-Barr virus and cytomegalovirus [41,42].

- Excessive amounts of DNA from oral bacteria such as *Porphyromonas gingivalis* are present in the gingiva of patients with periodontitis [12] and in the synovial membrane from patients with RA [49,50] and may promote citrullination of various self-antigens [51].

- Strong correlation (2.6-fold risk increase) between presence of anti-CCP antibodies and presence of periodontitis in patients with RA [53].

- Presence of Gp-39 (cartilage antigen targeted by the autoimmune response in rheumatoid synovitis) in gingival tissue [54].

- Key role for B cells and plasma cells in chronic inflammation of gingival and synovial tissues.

- Mechanism underlying alveolar resorption similar to the mechanism involved in joint erosions.

ondary Sjögren syndrome, and neither does primary Sjögren syndrome increase the prevalence of periodontitis [3,10,11]. The similar prevalence of periodontal disease in patients with and without sicca syndrome may be ascribable in part to the lack of an association between oral dryness and presence of organisms associated with periodontal disease (*P. gingivalis*, *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Treponema denticola*, *Eikenella corrodens*, *Campylobacter rectus*, *Bacteroides forsythus*, and *Streptococcus oralis*) [11]. The similar severity of periodontal disease in patients with and without sicca syndrome suggests that the pathogenesis of periodontal bone resorption may share similarities with that of bone erosions in rheumatoid joints. Further support for this possibility comes from the absence of joint erosions in patients with arthritis related to Sjögren syndrome.

4. Pathogenic factors shared by rheumatoid arthritis and periodontal disease: the immune response, including B-cell overactivity

The gingival tissue affected with periodontitis exhibits increased angiogenesis, which is also a feature in the rheumatoid synovium. Neutrophils are the predominant cell type in both joint fluid and crevicular fluid. However, neutrophils contribute less than 5% of cells in the gingival tissue [12], where other cell types involved in innate and adaptive immunity play a far greater role in perpetuating the inflammatory process and subsequent alveolar resorption. Macrophages [13] release numerous cytokines, thereby promoting vessel hyperplasia (gingival bleeding) and an influx of other cell types involved in immune responses. Then, dendritic cells, most notably those stimulated by *P. gingivalis* [14], promote lymphocyte activation, perpetuating B-cell overactivity [13]. Thus, gingival tissue affected with periodontitis contains a larger proportion of B cells than of T cells [12]. Some of the T cells exhibit a regulatory phenotype (Treg), and the percentage of $CD4^+CD25^{\text{high}}$ Treg cells increases with lesion severity and with the proportion of B cells relative to T cells [15]. Despite the presence of Treg cells, the levels of regulatory cytokines such as IL-4 and IL-10 in crevicular fluid from RA patients are usually low, and the lowest levels are found in patients with severe periodontitis.

The presence of a strong B-cell response (with 15% of B cells as a proportion of immune cells compared to 7% of T cells) [16] is related not only to T helper effects [12], but also to the gingival epithelium, which enhances B-cell survival and B-cell maturation to plasma cells. This last effect may explain the occurrence of gingival plasmacytomas [17]. Plasma cells contribute up to 50% of gingival cells in some cases of periodontitis [12] (Fig. 1), which explains the high levels of IgA and IgG found in crevicular fluid (IgM tends to remain bound to the gingival epithelium at sites of periodontitis) [18]. These antibodies exert chiefly beneficial effects as they contribute to control bacterial growth via neutralization, opsonization, or complement activation. In contrast, B-cell overactivity may produce chiefly deleterious effects on the periodontium [19], as B cells are the most effective cells in presenting antigens to T cells in gingival tissue affected with periodontitis [20–22]. This antigen presentation may cause excessive release of RANK-L (Fig. 1) or cytokines capable of promoting osteoclastogenesis.

Most studies involving cytokine assays found that IL-1 β levels in crevicular fluid correlated closely with periodontitis severity [23]. However, this correlation was absent in some studies, most notably in periodontitis associated with RA [24], as IL-1 β levels in crevicular fluid (within the periodontal pockets) were elevated at active sites but not at inactive sites ($P < 0.05$) [13]. It has been suggested that specific IL-1 β polymorphisms may promote the development of periodontal disease. However, a study of 100 non-RA patients with severe periodontitis, 100 RA patients including 86 with periodontitis, and 100 healthy controls found no increase in the prevalence of IL-1 β polymorphisms in patients with periodontitis [25]. High levels of IL-17 were found in crevicular fluid from periodontal pockets from 16 patients with periodontitis and eight controls (45.9 pg versus 35.6 pg, $P = 0.005$) [26]. Given that IL-17 promotes osteoclastogenesis, excess amounts of IL-17 may contribute to alveolar resorption (Fig. 1). However, in mice lacking the IL-17 receptor, exposure to organisms such as *P. gingivalis* led to increased periodontal bone destruction [27]. IL-17 is crucial in the protection against extracellular pathogens and therefore may play a dual role in periodontitis, improving pathogen control but also promoting alveolar resorption when released in excessive amounts.

5. Pathogenic factors shared by rheumatoid arthritis and periodontal disease: bone resorption

Studies of crevicular fluid from healthy individuals and patients with chronic periodontal disease established that RANK elevation was a specific feature of periodontitis, being present neither in healthy individuals nor in patients with gingivitis [28]. RANK-L levels were also elevated in gingival tissue from patients with periodontal disease [29]. The severity of periodontal disease correlates somewhat with RANK-L and osteoprotegerin overexpression [30] and more strongly with the RANK-L/osteoprotegerin ratio [31].

In some murine models of periodontitis, T cells seem to be the main source of RANK-L [32]. However, gingival B cells can express large amounts of RANK-L at their surface (Fig. 1), which may suffice to induce bone resorption. In an athymic rat model of periodontitis induced by *A. actinomycetemcomitans*, B-cell clones specific of this organism exhibited the highest surface expression of RANK-L, and this expression was sufficient to induce bone resorption via a mechanism that was inhibited by osteoprotegerin [33].

In human gingival tissue, only 20% of B and T cells express RANK-L in normal individuals compared to 50% of T cells and up to 90% of B cells in patients with periodontitis [29]. Therefore, the impact of rituximab therapy on the course of periodontitis may deserve investigation, particularly as B cells may stimulate osteoclasts via other pathways such as IL-17 oversecretion, with upregulation by IL-6 [34].

Among the components of the oral flora, some organisms such as *P. gingivalis* may be strong inducers of RANK-L expression. *P. gingivalis* counts correlated with RANK-L levels in a study of 15 patients with periodontitis and 15 healthy individuals [35]. *P. gingivalis* does not induce osteoprotegerin elevation. In another study, adding *P. gingivalis* increased the RANK-L/osteoprotegerin ratio in cultures of gingival fibroblasts and periodontal ligaments [36]. An amino acid sequence similar to the Arg-gingipain cysteine proteases may be involved in RANK-L production, as *P. gingivalis* strains carrying Lys-gingipain mutations fail to increase RANK-L levels [36].

Conventional immunosuppressants may induce greater osteoprotegerin elevation than RANK-L downregulation [31], which may slow the progression of periodontal disease. Similar effects may occur with TNF α antagonists. Thus, a marked decrease in serum RANK-L levels has been reported after infliximab therapy for RA [37]. However, this effect of TNF α antagonists has not yet been confirmed, and the potential of these agents for increasing bacterial growth may promote the development of some forms of gingivitis [38]. Support for this hypothesis comes from a murine model of periodontitis induced by *A. actinomycetemcomitans* [39]. Mice lacking the p55 TNF α receptor had less bone resorption and lower levels of RANK-L expression but also exhibited decreased migration of lymphocytes, macrophages, and neutrophils, which resulted in increased proliferation of *A. actinomycetemcomitans* [39].

6. Pathogenic factors shared by rheumatoid arthritis and periodontal disease: smoking, herpes viruses, and bacteria (Box 1)

Smoking aggravates RA and also worsens periodontal disease by promoting bacterial growth. In a study of patients with periodontitis including 88 untreated smokers, 90 untreated nonsmokers, 171 treated smokers, and 119 treated nonsmokers, smoking was associated with increased levels of *B. forsythus*, *Peptostreptococcus micros*, *F. nucleatum*, and *C. rectus* [40].

Another factor associated with bacterial growth may be prior infection with the Epstein-Barr virus 1 (EBV-1) and cytomegalovirus, which promote gingival colonization with *P. gingivalis*, *A. actinomycetemcomitans*, *B. forsythus*, *P. intermedia*, *Prevotella nigrescens*, or *T. denticola* [41]. The strongest association links the presence of EBV in gingival tissue and co-infection with *P. gingivalis* (OR, 3 to 6 depending on whether other bacteria are also present) [41,42]. This association may explain the close link between the presence of EBV-1 and/or cytomegalovirus and the development of severe periodontitis. In a study involving PCR testing of gingival tissue in 140 adults, the OR for periodontitis was 5 when EBV-1 was identified and 3 to 5 when cytomegalovirus was found [41]. Similarly, EBV was found in 71% to 89% and cytomegalovirus in 65% to 78% of patients with severe periodontal disease, compared to 6% for EBV and 0% for cytomegalovirus among controls without periodontal disease [43].

A study of the bacterial profile in periodontal pockets of 116 patients with periodontal disease (mean age, 40 years) indicated overrepresentation of various organisms including *P. gingivalis*, *A. actinomycetemcomitans*, *P. intermedia*, *B. forsythus*, *F. nucleatum*, and *P. micros* [44]. The ORs were highest for *P. gingivalis* (12.3) and *B. forsythus* (10.4) [44]. In a study of 78 patients with periodontal disease, 86% of patients had at least one of the following bacteria in their periodontal pockets: *P. gingivalis*, *A. actinomycetemcomitans*, *P. intermedia*, *C. rectus*, and *P. micros* [45]. In addition, yeasts were found in 12 (15%) patients, staphylococci in seven (9%), and intestinal bacteria in six (8%) [45].

Direct recovery of these organisms via microbiological methods such as PCR testing probably has greater validity than serologi-

cal studies. Data on correlations between antibody titers against various oral bacteria and the presence or severity of periodontal disease are somewhat conflicting. Thus, correlations were found for antibodies to *P. gingivalis* [4,46], most notably in older smokers, whereas correlations were weak or absent for antibodies to *A. actinomycetemcomitans* [46], *B. forsythus*, *C. rectus*, and *P. intermedia* [4]. Furthermore, serum antibody levels do not consistently correlate with antibody levels at other sites such as joint fluid. We investigated the IgG and IgA antibody responses to *P. gingivalis*, *P. intermedia*, *B. forsythus*, and *Candida albicans* in sera ($n=116$) and joint fluid ($n=52$) from patients with RA, joint fluid from patients without RA ($n=43$), and sera from blood donors ($n=100$) [47]. Titers of antibodies to *P. gingivalis* were not significantly different between the RA samples and the control samples. In contrast, titers of IgG and IgA antibodies to *B. forsythus* were higher in joint fluid samples from patients with and without RA, whereas titers in sera were lower in RA patients than in blood donors [47]. This last finding suggests that the systemic antibody response may be too weak to prevent the dissemination of some microorganisms and the progression of some forms of periodontal disease. In keeping with this possibility, serum antibody titers to several microorganisms declined in 43 adults experiencing progression of periodontal disease despite local care [48].

Several studies evaluated periodontal bacterial DNAs in synovial fluid from patients with inflammatory joint disease. For instance, in a study of 19 patients with RA and periodontal disease, periodontal bacterial DNA was found consistently in synovial fluid (*P. intermedia* in 73% and *P. gingivalis* in 42%) [49]. Serum and joint fluid from 16 patients with RA, 14 with psoriatic arthritis, and nine with osteoarthritis were tested for 40 oral bacterial DNAs [50]. In sera, the mean number of species was 6.2 ± 3.2 in the RA group, 5.4 ± 2.7 in the psoriatic arthritis group, and 2.1 ± 1.7 in the osteoarthritis group. In joint fluid, the numbers were higher, 14.0 ± 6.8 in RA and 19.4 ± 7.1 in psoriatic arthritis compared to 4.0 ± 1.7 in osteoarthritis [50]. *P. gingivalis*, *Tannerella forsythensis*, and *P. intermedia* were not found in the osteoarthritis group but were common in the RA and psoriatic arthritis groups. *P. gingivalis* and *P. nigrescens* were found only in RA patients [50]. These data suggest that migration of DNA from oral bacteria to the synovial membrane may be a common event, despite the presence of an antibody response. However, migration was also found in patients with osteoarthritis, although migration of some organisms such as *P. gingivalis* and *P. intermedia* seemed more specific of RA.

7. Pathogenic factors shared by rheumatoid arthritis and periodontal disease: loss of tolerance to citrullinated antigens? (Box 1)

P. gingivalis produces the enzyme peptidylarginine deiminase (PAD) that is responsible for citrullination of various self-antigens [51]. According to one hypothesis, loss of tolerance to citrullinated antigens (with the production of anti-CCP antibodies) may be initiated or perpetuated in the periodontium by *P. gingivalis* infection. A single study found no correlation between the presence of periodontitis and the presence of anti-CCP antibodies [52]. The presence of the HLA-DR shared epitopes (which are overrepresented in patients with periodontitis [8]) correlates with high anti-CCP levels. Other studies found a close correlation between the presence of anti-CCP antibodies and the presence of periodontitis in patients with RA [53]. For instance, among 6616 patients evaluated for periodontitis in 1996–1998 as part of a prospective study on the subsequent risk of atheroma (ARIC cohort), 33 developed RA, including 27 with and only six without periodontitis. In adjusted analyses, periodontitis remained associated with RA, the relative risk being 2.6. In a study of patients with RA, anti-CCP titers

were considerably higher in patients with moderate to severe periodontitis than in patients without periodontitis (223 versus 8 U) ($P=0.04$) [53]. Loss of tolerance to citrullinated antigens induced by the presence of *P. gingivalis* in periodontitis lesions is further supported by the detection of citrullinated proteins in the periodontium of 6/15 and 7/15 patients with periodontitis, as well as in healthy individuals, and by the presence in gingival tissue of the enzyme peptidylarginine deiminase type 2 [54].

P. gingivalis may be able to induce apoptosis of some lymphocytes and to alter the T-cell response via the expression of superantigens. Furthermore, *P. gingivalis* DNA is often found in synovial samples from patients with RA. These data suggest that *P. gingivalis* may play a central role in inducing or perpetuating RA in some patients [55]. Another self-antigen targeted by the immune system in RA patients (Gp39) is also present within the gingiva [54]. Further research is needed to determine whether an increased response to *P. gingivalis* is sufficient to induce anti-CCP production and, perhaps, RA. The presence of *P. gingivalis* DNA in the synovium may be a mere epiphenomenon related to DNA trapping by the synovial filter. Studies involving exposure to *P. gingivalis* of mice transgenic for the human shared epitope might provide valuable data. Another possibility is that loss of tolerance to citrullinated antigens may develop only in patients with prior or concomitant deficiencies in the naturally occurring Treg cells that control the immune response in the gingiva. During embryogenesis, the origin of the gingival epithelium is similar to that of the thymic medulla, where education of naturally occurring T cells takes place [56].

8. Conclusion

Referral for dental care on at least one occasion is probably in order for patients with RA, most notably those who have anti-CCP antibodies and preferably early in the course of the disease. Randomized trials in small numbers of RA patients [57], some of whom were taking TNF α antagonists [58], indicate that this strategy is beneficial. Furthermore, appropriate treatment of periodontitis may decrease the risk of subsequent atheroma. Thus, several studies found that the prevalence of periodontitis correlated with the prevalence of coronary artery disease, particularly in RA patients [59]. Furthermore, the presence of severe periodontitis may indicate a need, not only for referral for dental care, but also for initiating biological therapy. Serum TNF α antagonist levels correlated with periodontitis severity in RA patients, and TNF α antagonist therapy may have a favorable impact on the course of periodontitis, although the relevant studies were conducted in small sample sizes. In one study, infliximab therapy in 10 RA patients was associated with a small decrease in periodontitis and with lower crevicular fluid TNF α levels, compared to 10 RA patients without TNF α antagonist therapy [60]. The impact of infliximab therapy on periodontitis was evaluated in 40 patients with RA [38]. Attachment loss was decreased after infliximab therapy (prevention of “structural” lesions). However, infliximab therapy failed to diminish the gingival inflammation, perhaps because the antiinflammatory effects were partially counteracted by increased bacterial growth in the periodontal pockets.

Conflict of interest statement

The authors have no conflict of interest to declare.

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