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# Lessons to be learned from periodontitis

*Koen M.J. Janssen*[a], *Arjan Vissink*[a], *Menke J. de Smit*[b], *Johanna Westra*[c], *and Elisabeth Brouwer*[c]

**Purpose of review**
This article reviews the link between periodontitis and rheumatoid arthritis (RA) with regard to similarities in genetic risk factors and immunopathogenesis. Emphasis is paid to the potential role of the periodontal pathogen *Porphyromonas gingivalis* in the etiopathogenesis of both periodontitis and RA, in particular by post-translational modification of arginine into citrulline.

**Recent findings**
*P. gingivalis*, a major periodontal pathogen, is presently known as the only bacterium in the oral flora which contains a peptidyl arginine deiminase enzyme (PAD). This enzyme is necessary for citrullination. As a result, citrullinated proteins and *P. gingivalis* PAD, PAD2 and PAD4 (expressed by infiltrating neutrophils) are found in periodontal tissues. Autoantibodies directed to citrullinated proteins, so-called anticitrullinated protein antibodies (ACPAs), are found to be present in gingival crevicular fluid originating from inflamed gingival tissue. Furthermore, treatment studies have revealed that nonsurgical periodontal treatment, that is removal of sub-gingival calculus and biofilm deposits, is accompanied by a reduction in the severity of RA.

**Summary**
In this study the similarities in immune response and tissue degradation between RA and periodontitis are reviewed. It is shown that the two diseases share the same environmental and genetic risk factors, apart from the fact that there is a link between both diseases via citrullination of proteins by human PAD and *P. gingivalis* PAD.

**Keywords**
citrullination, peptidyl arginine deiminase, periodontitis, *Porphyromonas gingivalis*, rheumatoid arthritis

## INTRODUCTION

Periodontitis is an infective process which ultimately leads to the destruction of the soft and hard tissue that supports the teeth (the periodontium). Periodontitis has been associated with a number of chronic and inflammatory diseases such as diabetes mellitus [1], atherosclerosis, cardiovascular disease [2], Crohn's disease and ulcerative colitis [3]. In the past decade the interest in the epidemiological and pathological relationships between periodontitis and rheumatoid arthritis (RA) has been rising [4]. This is not surprising as RA and periodontitis share the same genetic risk and environmental factors and also both diseases are age-associated and characterized by chronic self-sustaining inflammation. Therefore, the aim of this study is to provide a review of the etiopathogenesis of periodontitis, focusing on aspects that may be of relevance for RA.

## PERIODONTITIS

The periodontium is composed of specialized tissues, viz. the gingiva, periodontal ligament, cementum and alveolar bone. Chronic inflammation of these tissues, initiated by bacteria, gradually results in bleeding gums, deepened periodontal pockets and ultimately in loss of alveolar bone, and mobility and loss of teeth (Fig. 1) [5–7]. The prevalence of periodontitis in an adult population is 10–15%, independently of ethnicity and geographic location [8]. Periodontitis can be classified as chronic (slowly progressive) and aggressive (highly destructive) periodontitis. Periodontitis can also be classified on the basis of the extent (localized/generalized) and severity (mild/moderate/severe) of the disease [9].

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## KEY POINTS

- Rheumatoid arthritis (RA) and periodontitis share common genetic and environmental risk factors.
- The periodontal pathogen, *P. gingivalis*, is presently known as the only bacterium in the oral flora which contains a peptidyl arginine deiminase enzyme (PAD).
- Anticitrullinated protein antibodies (ACPAs) are found to be present in gingival crevicular fluid (GCF) originating from inflamed gingival tissue.
- Treatment studies have revealed that nonsurgical periodontal treatment is accompanied by a reduction in the severity of RA.

Genetic and lifestyle factors determine the susceptibility of a person to periodontitis. A significant genetic factor for severe periodontitis is a variation in the major histocompatibility complex, class II, DR beta 1, (HLA-DRB1) SE [10]. Furthermore, several single-nucleotide polymorphisms, especially in interleukin (IL)-1, IL-6 and IL-10, vitamin D receptor, and CD14 genes have been associated with the severity and presence of destructive periodontal disease. In addition, smoking has been considered an important lifestyle factor contributing to the susceptibility of periodontitis [11]. The contributory effect of smoking is thought to be the effect of nicotine on the induction of pro-inflammatory cytokines [12] and activation of matrix metalloproteinase-3 (MMP-3) [13].

## IMMUNE RESPONSE IN PERIODONTITIS

The innate immune response in periodontitis is involved in the elimination of microbial challenges, and also may result in damage to the periodontium. The host has certain mechanisms to maintain a nonirritating environment for the bacterial flora, like the washing effect of saliva and gingival crevicular fluid (GCF), and the phagocytic action of neutrophils that migrate continuously through the junctional epithelium into the pocket. When pathogenic bacteria overcome these protecting barriers and start to populate the periodontal area, the release of bacterial toxins and metabolites by these bacteria will activate the innate immune system. Upon this bacterial driven challenge, epithelial cells will respond and start to secrete pro-inflammatory cytokines such as IL-1β, tumor necrosis factor (TNF-α), IL-6 and IL-8 [14]. When the inflammation persists, tissue destruction will occur, for example, by MMPs. These MMPs are responsible for the destruction of the collagenous extracellular matrix.

Inflammation in periodontitis is characterized by a large influx of leukocytes in the periodontal lesions. The innate immune response is characterized by activation of resident cells (dendritic cells, epithelial cells and endothelial cells) and migration of neutrophils, monocytes and macrophages. The adaptive immune response includes the influx of T and B cells in the lesions. Plasma cells comprise about 50% of the cells, B cells represent about 18% of the cells and T cells represent a smaller proportion than B cells [15]. The proportion of B cells compared with T cells increases further when taken from sites with severe periodontitis [15]. In addition, a high proportion of the CD19 B-cell population in the peripheral blood (40–50%) in periodontal susceptible patients was shown to bear features of the B-1a subtype (CD5CD19 double positive) compared with 15% in healthy controls. These B-1a B cells are known to be associated with the production of (auto-)antibodies [15].

## RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic auto-inflammatory polyarthritis with a prevalence of 0.5–1.0% in the adult population. RA is more frequent among women than men (3 : 1) and its prevalence, like periodontitis, rises with age [16]. RA is known to develop in genetically susceptible individuals under certain environmental conditions. Years before start of the synovial inflammation in RA, autoantibodies as rheumatoid factor and anticitrullinated protein antibodies (ACPAs) are found to be present in conjunction with elevated cytokines in nonsymptomatic so-called arthritis risk patients [17,18].

After the first stage (activation of the innate response) and the second stage (activation of the adaptive response) the third stage of the disease is known as the destructive phase. Longstanding destructive RA is characterized by synovitis, fibrous deposition and damage of the cartilage, erosions of the subchondrial bone and periosteal soft tissue inflammation (Fig. 1). Immune responses with several inflammatory cascades lead towards this final common pathway characterized by a persistent inflammatory infiltrate in the synovial membrane of the joints [5]. Presently a large effort is being made to diagnose RA as early as possible [19]. Early aggressive treatment in the so-called window of opportunity leads to less damage and sometimes even to remission of RA [20].

## IMMUNE RESPONSE IN RHEUMATOID ARTHRITIS

Presently activation of the innate immune system by an environmental trigger, probably infection-related, is thought to start the inflammatory loop



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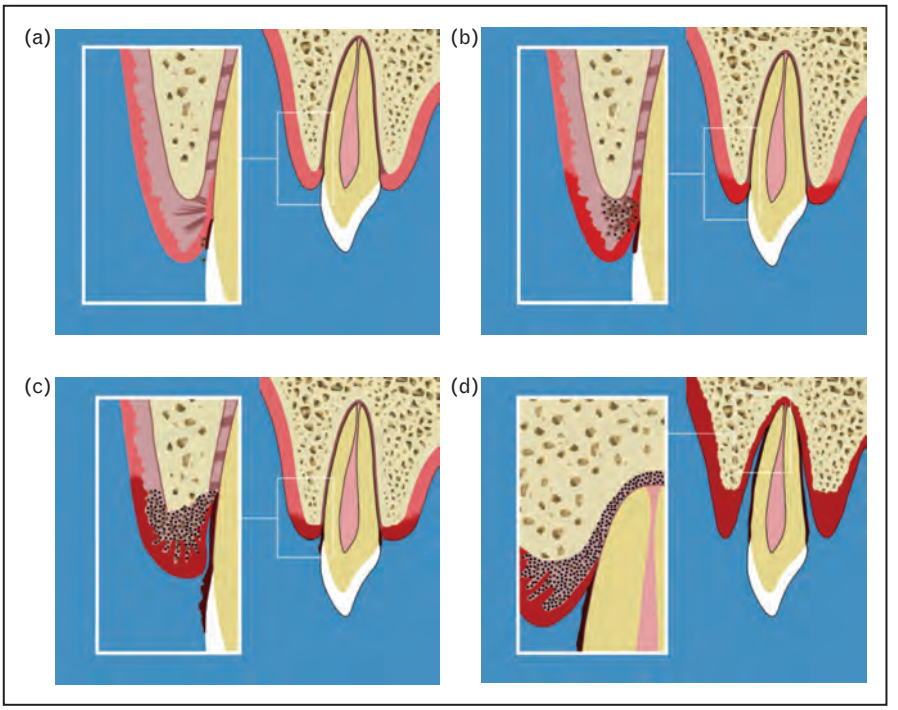


**FIGURE 1.** Sequential stages in the development of periodontitis (a–d) and arthritis (e–h). (a) The periodontium is composed of specialized tissues, viz. the gingiva, periodontal ligament, cementum and alveolar bone. Healthy gingiva is characterized by a continuous sparse migration of neutrophils into the coronal part of the epithelium. (b) Gingivitis will develop when the microbial colonization has evolved to such a level that microbial products evoke a more substantive inflammatory response. This response is characterized by an increased infiltration and migration of neutrophils, lymphocytes and monocytes and macrophages. Very few plasma cells are noted within the expanding lesion. Degeneration of fibroblasts and collagen breakdown occurs. (c) Continuation of the exposure of the periodontal tissues to microbial biofilm, which moves apically, results in a further enhancement of the inflammatory response of the gingival tissue. The inflammatory cell infiltrate extends further apically and is now dominated by plasma cells. Collagen loss continues. The epithelium has become more permeable and may be ulcerated. (d) The biofilm continues its apical down-growth. The inflammatory cell infiltrate extends in to the periodontal attachment. Plasma cells comprise about 50% of the cells, B cells represent about 18% of the cells and T cells represent a smaller proportion than B cells. The immunopathological tissue damage by matrix metalloproteinases results in loss of alveolar bone, mobility of teeth and finally in tooth loss. (e) The normal joint is composed of cartilage, bone and a synovial membrane containing an outer layer or subintima (fibrous, fatty or loosely areolar) and an inner lining layer. This inner layer consists of two cell types: type A derived from blood monocytes, and type B which is dominated by fibroblasts producing synovial fluid. Synovial fluid is made of hyaluronic acid and lubricin, proteinases, and collagenases. (f) Activation of the innate immune system by an environmental trigger, probably infection-related, is thought to start the inflammatory loop in RA. Processing of an unspecified not necessarily rheumatoid autoantigen by dendritic cells and presentation to T cells with a co-stimulatory signal can further activate T cells. The presentation of the antigen probably takes place in the central lymph nodes. T cells subsequently become clonally expanded and migrate to the (synovial) tissue where they interact with synoviocytes, B cells and macrophages and thus promote inflammation [5] as part of the adaptive immune response. In addition, as a person ages, the water content of the cartilage decreases as a result of a reduced proteoglycan content, thus causing the cartilage to be less resilient. Without the protective effects of the proteoglycans, the collagen fibers of the cartilage can become susceptible to degradation and thus exacerbate the degeneration. Breakdown products from the cartilage are released into the synovial space, and the cells lining the joint attempt to remove them resulting in inflammation. (g) At a later stage in the adaptive arm of the immune response the synovial tissue of RA patients is characterized by infiltration and activation of mononuclear cells (including T and B lymphocytes, plasma cells, dendritic cells and macrophages) [6]. B cells present antigens to T cells and produce pro-inflammatory cytokines and autoantibodies which stimulate the production of pro-inflammatory cytokines by the formation of immune complexes and activation of macrophages. Both T and B-cell activation results in increased production of cytokines, chemokines and MMPs, which activates a positive feedback loop perpetuating the autoimmune inflammatory response [7]. (h) Longstanding destructive RA is characterized by synovitis, joint space narrowing, fibrous deposition and damage of the cartilage, erosions of the subchondrial bone and periosteal soft tissue inflammation.



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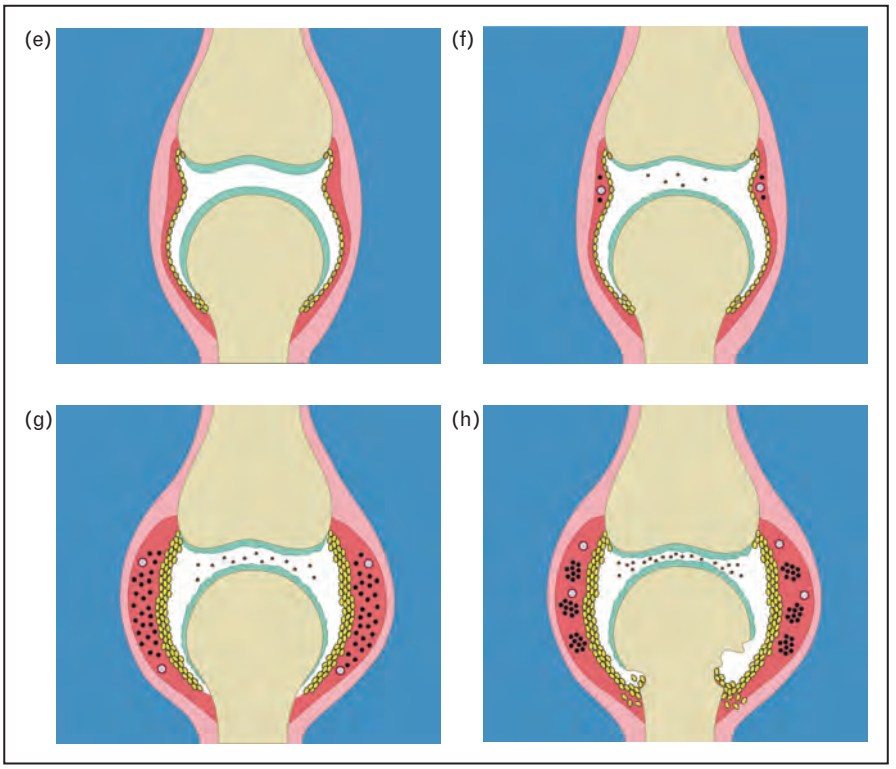


**FIGURE 1.** (*Continued*)

in RA. Processing of an unspecified not necessarily rheumatoid autoantigen by dendritic cells and presentation to T cells with a co-stimulatory signal can further activate the T cells. The presentation of the antigen probably takes place in the central lymph nodes. T cells subsequently become clonally expanded and migrate to the (synovial) tissue where they interact with synoviocytes, B cells and macrophages, and thus promote inflammation. Loss of tolerance in the inflammatory environment can induce an auto-immune response [5]. At a later stage the synovial tissue of RA patients is characterized by infiltration and activation of mononuclear cells (including T and B lymphocytes, plasma cells, dendritic cells and macrophages) [6]. B cells present antigens to T cells and produce pro-inflammatory cytokines and autoantibodies which stimulate the production of pro-inflammatory cytokines by the formation of immune complexes and activation of macrophages. Both T and B-cell activation results in increased production of cytokines, chemokines and MMPs, which activates a positive feedback loop perpetuating the auto-immune response [7].

The synovial fluid in RA patients is rich in pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-15, and IL-17. The same pro-inflammatory cytokines are found to be up-regulated in periodontitis lesions [21]. In addition, tissue destruction in RA takes place via, for example, MMPs which is similar to the breakdown of periodontal tissue in periodontitis patients. Furthermore, RA is linked to the same genetic variations in the major histocompatibility complex (HLA-DRB1) as observed in periodontitis. Likewise, smoking is considered as a lifestyle risk factor in RA and periodontitis [22]. Contrary to periodontitis where smoking is found to directly affect the periodontium, in RA it is thought that the induction of citrullinated proteins by smoking can contribute to the autoimmune response [23].

## CITRULLINATED PROTEINS

The majority of individuals (50–80%) with RA are found to be seropositive for autoantibodies [24]. Rheumatoid factor, antibodies which bind to the constant domain of the IgG molecule, and ACPAs, antibodies against citrullinated proteins, are the most common autoantibodies in RA [25]. Autoantibodies against citrullinated proteins include anti-citrullinated vimentin, anticitrullinated filaggrin, anticitrullinated fibrin(ogen) and anticitrullinated α-enolase antibodies [26]. Seropositivity to these autoantibodies often precedes the clinical onset of the disease [27]. ACPAs have a higher diagnostic sensitivity and specificity for RA than rheumatoid factor [24], since a number of rheumatic and



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nonrheumatic diseases are associated with a positive rheumatoid factor [25]. Presence of ACPAs seems to be associated with a poorer disease outcome [28].

Autoimmunity to citrullinated proteins is rather specific for RA since ACPAs are found in 1–2% of the normal population and are rare in other inflammatory conditions [29]. Remarkably, two studies [30,31] reported that the incidence of ACPAs is higher in patients with severe periodontitis (~8%). ACPAs are also present in GCF of periodontitis patients [32▪▪].

Citrullination is a process that occurs during inflammation in a wide range of tissues by an enzyme known as peptidylarginine deiminase (PAD). This enzyme can generate post-translational modifications by exchanging protein-bound arginine for citrulline, a nonstandard amino acid, thereby changing the charge of the target protein and therefore altering its structure and function. In humans, five isotypes of PAD have been described. Human PAD enzymes are calcium-dependent; therefore they are likely to be active in the extracellular fluid. PAD2 and PAD4 have been found in inflamed synovial tissue of RA patients [33] and are therefore likely involved in the citrullination of synovial proteins in RA.

Recently, PAD2 and PAD4 expression [32▪▪] and the presence of citrullinated proteins [32▪▪,34▪▪] have been found in inflamed periodontal tissue. Thus, citrullination of proteins in periodontal tissue is associated with inflammation, which is in accordance with other sites of the human body [35,36]. The study by Nesse *et al.* [34▪▪] showed that citrullination of proteins was not solely observed in inflamed tissue from periodontitis patients but also in inflamed tissue of nonperiodontitis origin (e.g. pericoronitis tissue). The citrullination in periodontitis resulted in additional types of citrullinated proteins that were not observed in noninflamed periodontal tissue [34▪▪]. These additional types of citrullinated proteins showed a striking similarity with citrullinated proteins found in the synovium of RA patients, indicating that the same proteins might get citrullinated in periodontitis and RA-affected synovial tissue [34▪▪].

## PORPHYROMONAS GINGIVALIS

One of the best known periodontal pathogens in the bacterial biofilm, that covers the subgingival area and is causing the inflammatory response, is the prokaryote *Porphyromonas gingivalis (P. gingivalis)*, an anaerobic Gram-negative bacterium. The prevalence of *P. gingivalis* in severe periodontitis is 70%. *P. gingivalis* is infrequently isolated from individuals without periodontitis [37]. This bacterium is of particular importance as it is the only known bacterium that has its own PAD enzyme. Although *P. gingivalis* PAD has a sequence dissimilar from that of human PAD, *P. gingivalis* PAD is able to citrullinate its endogenous proteins [38]. In contrast to human PAD, *P. gingivalis* PAD is not calcium-dependent [39]. In addition, the enzyme is able to citrullinate human fibrinogen and α-enolase [40]. Thus, it is possible that *P. gingivalis* PAD citrullinates proteins from its host, thereby creating systemic immunogens that contain epitopes against which ACPAs could be raised [41]. An important observation in this respect was the presence of oral bacterial DNAs in the synovial fluid of RA patients, amongst which is *P. gingivalis* [42], while *P. gingivalis* DNA was not found in synovial fluid of healthy controls. This observation supports the potential role of *P. gingivalis* PAD in citrullination of synovial proteins.

Recently, the relation between *P. gingivalis* and RA has been assessed in a number of studies. Patients with RA showed significantly higher levels of anti-*P. gingivalis* antibodies in serum than healthy controls [43,44]. The same holds true for individuals at risk for RA [45]. It was also observed that anti-*P. gingivalis* levels were found to be higher in ACPA-positive patients than in ACPA-negative patients [44]. These observations need further study as Scher *et al.* [46▪] recently showed that *P. gingivalis* colonization in the subgingival area for new-onset RA patients was comparable to chronic RA patients and controls with a comparable level of periodontitis. The latter study also showed that the presence of *P. gingivalis* did not correlate with ACPA titers. Their findings are supported by the observations of De Smit *et al.* [47] who reported that occurrence of *P. gingivalis* in the subgingival area was not different between RA patients and non-RA controls.

## EPIDEMIOLOGICAL STUDIES INDICATING AN ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS AND PERIODONTITIS

In recent years, a number of studies reported a higher prevalence of periodontitis in patients with RA compared with non-RA controls [48–51] and a higher prevalence of RA in patients with periodontitis compared with nonperiodontitis controls [52]. Pischon *et al.* [48] examined 57 patients with RA and 52 healthy controls and assessed these patients on plaque index, gingival index, pocket probing depth and clinical attachment loss. Patients with RA turned out to have a significantly increased



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periodontal attachment loss compared with controls. Dissick *et al.* [49] found a higher prevalence of periodontitis in a cohort of RA patients (69 patients) compared with a cohort of osteoarthritis patients (35 patients). The historical cohort study by Torkzaban *et al.* [50] evaluated 53 patients with RA and 53 individuals without RA and found a significant correlation between RA and bleeding on probing, and between RA and clinical attachment loss. However, no significant correlation between RA and plaque index could be found. Recently, Chen *et al.* [51] investigated the association between the risk of RA and the history of periodontitis in a nationwide, population-based control study. This study was based on administrative data and estimated the odds ratio for RA development on the basis of periodontitis history. An association was found (odds ratio 1.16), albeit a weak association. Nesse *et al.* [52] found an increased prevalence of RA in patients with periodontitis that attended a dental or periodontal clinic. The increased incidence of RA in patients with periodontitis could not be explained by confounding factors. Other studies [53,54], however, did not report such an association. These conflicting data may be due to selection or recall bias and differences in RA and periodontitis classification criteria, patients' race, and study design [55].

## TREATMENT STUDIES INDICATING AN ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS AND PERIODONTITIS

The association between RA and periodontitis suggests that periodontal treatment may be beneficial in RA. Initial therapy for periodontitis is composed of mechanical removal of dental plaque and calculus [56]. A recent study by Erciyas *et al.* [57] showed that nonsurgical periodontal treatment comprising supragingival scaling, root planing and oral hygiene instructions reduced systemic inflammatory levels (ESR, CRP, TNF-α levels in serum) and DAS28 scores as assessed in periodontitis patients with low or moderate to highly active RA 3 months after nonsurgical periodontal treatment. This observation is in line with the results from other studies [58–60] showing that the severity of RA was reduced when RA patients with moderate/severe chronic periodontitis were treated with nonsurgical periodontal treatment. Furthermore, treatment of RA with disease-modifying antirheumatic drugs (DMARDS) was presumed to reduce the progression of periodontitis [60]. Therefore, the effect of anti-TNF-α therapy on the periodontal status of RA patients has been studied [60]. The results of this study showed no beneficial effect of anti-TNF-α therapy on the periodontal status of RA patients [60].

## CONCLUSION

The cause of periodontitis is multifactoral and shares similarities with RA. The main causative factor in periodontitis is the biofilm containing a number of bacteria affecting the periodontium by the release of pathogenic factors. Host factors such as immune response, smoking and poor hygiene are contributory factors, which also play a role in the etiopathogenesis of RA. *P. gingivalis*, the major periodontal pathogen may form a link between periodontitis and RA. *P. gingivalis* is the only known bacterium that has its own PAD enzyme and *P. gingivalis* PAD is able to citrullinate its endogenous proteins as well as human fibrinogen and α-enolase. Thus, *P. gingivalis* PAD can citrullinate proteins from its host, thereby creating systemic immunogens that contain epitopes against which ACPAs could be raised [41]. Present studies are ongoing to elucidate the connection between both diseases.

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### Conflicts of interest

*No conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 279).

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