## Commentary

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# Is there evidence indicating a link between periodontitis and rheumatoid arthritis?

"Even in the absence of a causal relationship ... these two diseases [periodontitis and rheumatoid arthritis] may still be inextricably interrelated through hitherto unidentified mutual mechanisms..."

Keywords: citrullination • periodontal pathogens • periodontitis • rheumatoid arthritis

An association between periodontal disease and rheumatoid arthritis (RA) has been recognized since ancient times when Hippocrates reported a cure for 'rheumatic troubles of the joints' by removal of diseased teeth [1]. Whether the patient had RA and whether the teeth removed were affected by periodontal disease remain unknown. More detailed documentation of a relationship between periodontal disease and rheumatoid arthritis began to appear at the beginning of the 20th century. Many of the early reports were anecdotal with limited description of the findings and the conclusions were based, at best, on a simplistic understanding of both diseases. During the mid 20th century, interest in the connection between these two diseases waned and it was not until the 1980s when case-control studies provided new evidence for a potential link between periodontal disease and RA. Since then, there has been considerable research effort directed toward investigating this relationship and the possible mechanisms that might be involved.

Both periodontitis and RA are heterogeneous chronic inflammatory diseases arising from a putative initiating factor and modified by genetic and environmental factors. While the initial trigger for periodontal disease is bacterial plaque accumulation on teeth, the trigger for RA is less clear.

In both RA and periodontal disease, inflammation within the affected tissues results in release of a huge array of proinflammatory cytokines from synovial cells in RA and keratinocytes, fibroblasts and osteoblasts in periodontal disease. These cells, together with infiltrating inflammatory cells (neutrophils, macrophages and lymphocytes) are key drivers of the extensive soft and hard tissue destruction noted in these two chronic inflammatory diseases.

Many case-control studies have reported a significant bidirectional relationship between periodontal disease and RA with regards to both incidence and severity [2,3]. A recent systematic review concluded that there is moderate-to-strong evidence to support the notion that there is a link between these two diseases and that common risk factors or common pathologic processes may be responsible [4]. However, most of these studies were limited by small sample sizes of 100 RA patients or less. A recent study investigating the relationship between periodontal disease and RA in 287 RA cases and 330 osteoarthritis controls [5] confirmed that RA patients with anti-citrullinated peptide antibodies (ACPA) were more likely to suffer from periodontal disease and that patients with periodontal disease were more likely to suffer from RA and also had higher ACPA and rheumatoid factor (RF) titers. These associations remained significant following multivariate analyses accounting for age, gender, smoking, HLA-DRB1 shared epitope positivity, race/ethnicity body mass index, self-reported diabetes marital status and education level. Further evidence that this association is independent of smoking, use of biological disease-modifying antirheumatic drugs (DMARDs) and plaque control has come from two studies investigating the prevalence of periodontal disease in early treatment-naive RA patients [6,7].



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To date, the literature highlights three important findings. First, individuals with severe RA are more likely to suffer from advanced periodontal disease and vice versa. Second, because control and RA patients have similar plaque scores and gingival bleeding indices, it is clear that oral hygiene is probably not impaired in RA patients despite the commonly held notion that reduced manual dexterity in RA patients impacts negatively on oral hygiene [5-9]. Third, the effect of medications taken for RA needs further consideration. Although many medications prescribed for RA (nonsteroidal anti-inflammatory drugs, corticosteroids, biologic DMARDs, etc.) significantly suppress inflammation, many RA patients still present with significant periodontal disease [8,10]. This observation indicates that the periodontal destruction probably became established well before the clinical onset of RA and subsequent prescription of inflammation-modifying drugs. This highlights that the duration of both periodontal disease and RA must be accounted for in future studies assessing the association between these two diseases.

On the basis of current clinical, biochemical and experimental evidence, several hypotheses have been proposed to explain the association between periodontitis and RA.

A role for infectious agents in the development of RA has been considered for over 70 years [11] so it is not surprising that there is interest in the role periodontal bacteria might play in the association between periodontitis and RA. Many of the periodontal pathogens comprising the subgingival microbiota have characteristics thought to be relevant to the risk of RA developing in genetically susceptible individuals. These include: induction of nonlethal low-grade infection; expression of proteins which share epitopes with the third hypervariable region of HLA-DRB10401 and HLA-DRB10101; persistence in the host resulting in chronic continuous lipopolysaccharide exposure and also the ability to form immune complexes with antibodies; cross-reactivity of antibodies to these pathogens with cartilage protein breakdown products and the ability to produce an anticartilage response and the capacity to citrullinate proteins leading to autoimmune responses. Thus it seems biologically plausible that peridontal pathogens have the capability to trigger or exacerbate RA in genetically susceptible patients.

Several studies have reported elevated levels of antibodies in serum and synovial fluid against periodontal pathogens RA patients compared with controls [12] and in others, DNA from periodontal bacteria has been identified in synovial fluid [13]. While such observations do not prove a causal role for these bacteria in the development of RA, they provide good evidence that periodontal pathogens have the potential to traverse from the periodontium to the joints. Whether this can then influence the inflammatory processes occurring within rheumatoid joints remains to be established.

Inflammation can result in degradation and structural change to proteins in the extracellular matrix. One such structural change is protein citrullination whereby the amino acid arginine is converted to citrulline. This process is mediated by the action of a family of enzymes known as peptidyl arginine deiminases (PAD). Citrullination results in the affected proteins becoming more immunogenic and the subsequent production of ACPA. The inflamed periodontium is considered an important site for citrullination and ACPA production [14]. ACPA have a high predictive value for RA, usually appearing several years before RA is evident clinically. The presence of these antibodies is also associated with more severe clinical outcomes for RA [15].

Therefore, production of ACPA as a result of extraarticular inflammation (e.g., during the development of gingivitis and periodontitis) prior to inflammation developing in the joints may be a critical step in the subsequent development of RA in susceptible patients.

In addition to the endogenous citrullination occurring as a result of periodontal inflammation, it is noteworthy that the periodontal pathogen Porphyromonas gingivalis is the only bacterium known to produce a PAD enzyme capable of causing protein citrullination [16]. The potential for PPAD to gain access to the periodontal connective tissues and cause protein citrullination provides a novel pathway for citrullination to occur in periodontitis patients [17]. Inoculation of mice with a PPAD-deficient strain of P. gingivalis reduced severity of experimental arthritis compared wild-type P. gingivalis [18,19]. However, whether PPAD is the essential link between periodontitis and RA is controversial with one report claiming that PPAD is not the link between RA and periodontal disease [20]. Other P. gingivalis related factors such as proteinases that degrade host proteins or activate other host inflammatory systems may be responsible for the co-existence of periodontal disease and RA [21].

Another mechanism by which periodontitis and RA may be inter-related is through the primed inflammatory response in the 'two-hit' model [22]. In this model, it is proposed that an initial 'hit' of chronic inflammation arising in the periodontal tissues is followed, at a later time, by a secondary inflammatory 'hit' in the joints to induce RA. This process then leads to an exaggerated inflammatory response that amplifies the inflammation and associated destruction in both periodontal and joint tissues. This relationship has been demonstrated experimentally in mice whereby induction of periodontal disease exacerbates the development of experimental arthritis and vice versa [23].

The clinical relevance of an association between RA and periodontitis relates to the potential impact on the management of patients who suffer from both conditions. However, the number of studies investigating the effect of nonsurgical periodontal treatment on disease activity in RA in patients with both periodontitis and RA has been limited. One systematic review concluded that there is some evidence to indicate that periodontal treatment can influence a number of biochemical and clinical markers of RA disease activity including erthryocyte sedimentation rate, levels of TNF-a, disease activity score and ACPA levels [24]. These studies were of short duration (6 months or less) and had low numbers of participants. Therefore, larger studies with longer follow-up periods are needed to determine whether nonsurgical periodontal treatment has any significant effect on clinical indicators of RA.

In conclusion, considerable research over the past 30 years has led to compelling evidence to confirm a link between periodontal disease and RA and there are good biological and clinical reasons for this to be more than circumstantial or mere association. While

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it should be noted that a case cannot be made for a causal role between these two conditions, this should not be totally discounted. This is especially relevant in light of recent findings that peridontal infection and inflammation can lead to production of ACPA capable of reacting with autoantigens from the joints leading to either initiation or modulation of rheumatoid arthritis. Even in the absence of a causal relationship, it should be noted that these two diseases may still be inextricably interrelated through hitherto unidentified mutual mechanisms leading to dysregulation of the immune and inflammatory systems resulting in similar disease processes manifesting in different parts of the body.

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## Commentary Bartold & Proudman

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