Periodontitis and Rheumatoid Arthritis: A Review

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Periodontitis and rheumatoid arthritis (RA) appear to share many pathologic features. In this review, the common pathologic mechanisms of these two common chronic conditions are explored. Emerging evidence now suggests a strong relationship between the extent and severity of periodontal disease and RA. While this relationship is unlikely to be causal, it is clear that individuals with advanced RA are more likely to experience more significant periodontal problems compared to their non-RA counterparts, and vice versa. A case is made that these two diseases could be very closely related through common underlying dysfunction of fundamental inflammatory mechanisms. The nature of such dysfunction is still unknown. Nonetheless, there is accruing evidence to support the notion that both conditions manifest as a result of an imbalance between proinflammatory and anti-inflammatory cytokines. As a result, new treatment strategies are expected to emerge for both diseases that may target the inhibition of proinflammatory cytokines and destructive proteases. The clinical implications of the current data dictate that patients with RA should be carefully screened for their periodontal status. J Periodontol 2005;76:2066-2074.

KEY WORDS
Arthritis, rheumatoid; periodontitis.

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“In fact, adult periodontitis and rheumatoid arthritis have much in common, so much so that I have argued that they are really the same disease.”

The above bold and challenging statement may seem to be stretching the boundaries of conventional thought too far. However, close inspection of two of the most common chronic diseases afflicting humans reveals remarkable similarities that warrant further investigation.

The relationship between rheumatoid arthritis (RA) and the progression of inflammatory conditions elsewhere in the body, such as periodontitis, is controversial. While a number of studies have presented conflicting results regarding a relationship between periodontitis and RA, there have been recent reports suggesting a significant association between these two common chronic inflammatory conditions. In light of these reports, there is a need for further investigations to determine whether the severity of RA and the severity of periodontitis are interrelated. To do this, controlled, population-based, laboratory, and clinical (molecular epidemiology) studies are needed to verify the immunological and biological associations between RA and periodontal disease.

PERIODONTAL DISEASES

The periodontal diseases range from the relatively benign form of gingivitis to aggressive periodontitis. Many of these conditions are not only a threat to the dentition, but may also be a threat to
general health. There are reports suggesting increased prevalence of diabetes, atherosclerosis, myocardial infarction, and stroke in patients with periodontal disease. This, thus, the likelihood of periodontal disease being associated with systemic diseases is becoming established fact. All forms of inflammatory periodontal disease are associated with chronic inflammation (accumulation of B and T lymphocytes as well as monocytes and neutrophils), resulting in destruction of the periodontal ligament and bone. If left untreated, significant tissue damage occurs, and the affected teeth can become loose and may be lost if the disease continues to be active. What is particularly curious about this disease is the great variability in presentation. Because of its multifactorial nature, which is modified by systemic, environmental, and microbiological factors, not all individuals are affected to the same degree despite the ubiquitous presence of dental plaque.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is also a chronic destructive inflammatory disease characterized by the accumulation and persistence of an inflammatory infiltrate in the synovial membrane that leads to synovitis and the destruction of the joint architecture resulting in impaired function. As a systemic disease, RA has extra-articular manifestations in systems such as the pulmonary, ocular, vascular, and other organs or structures that may be affected by the inflammatory process. The current paradigm for RA includes an initiating event (possibly a microbial exposure or a putative autoantigen) leading to significant synovial inflammation and tissue destruction. As for periodontal disease, there is an accumulation of inflammatory cells (T and B lymphocytes, neutrophils, and monocytes), tissue edema, endothelial cell proliferation, and matrix degradation. RA is also modified by systemic, genetic, and environmental variables.

SIMILARITIES BETWEEN RHEUMATOID ARTHRITIS AND PERIODONTITIS

Natural History

Periodontal disease. Natural history studies of periodontal disease in humans indicate the presence of three distinct subpopulations: 1) no progression of periodontal disease, in which around 10% of the population manifest very little or no disease which is of no particular consequence to the dentition; 2) moderate progression, affecting around 80% of the population and representing a very slowly progressing form of disease that generally can be easily managed via routine therapies; and 3) rapid progression, affecting approximately 8% of individuals whereby extensive periodontal destruction occurs which can be very difficult to control.

From the natural history studies of RA and periodontitis, it has been observed that certain RA and periodontitis populations are characterized by a particular type of patient who will experience disease progression irrespective of any treatment provided. Whether the RA group, in which disease progression seems uncontrolled even after comprehensive treatment, is the same group that is susceptible to develop severe forms of periodontal disease remains to be established and is, indeed, a major thesis of this review.

Rheumatoid arthritis. At least three types of disease manifestation can also be observed in RA populations: 1) self-limited: in these cases individuals originally presenting for RA have no evidence of disease 3 to 5 years later; 2) easily controlled: the disease is relatively easily controlled with only nonsteroidal anti-inflammatory drugs (NSAIDs); 3) progressive: these patients generally require second-line drugs, which often still do not fully control the disease.

Etiologic Factors

Periodontitis. The periodontal diseases are well recognized as classic examples of chronic inflammatory diseases resulting from the induction of host inflammatory responses to the subgingival biofilm. Gingivitis is typically characterized as a robust inflammatory response confined mainly to the superficial gingival connective tissues and is a relatively nonspecific response to a nonspecific accumulation of dental plaque. How gingivitis progresses to periodontitis is still unclear.

Periodontitis, on the other hand, appears to be a more specific inflammatory response to specific periodontal pathogens residing in the subgingival biofilm. Within the conditions known as periodontitis, there is considerable variability in terms of clinical manifestation and disease progression rates. This variability can be attributed to differences in composition of the subgingival microbial flora, as well as factors that modify the host response to the microbial challenge. Nonetheless, it must be noted that, although bacteria are necessary for disease initiation, they are not sufficient to cause disease progression unless there is an associated inflammatory response within a susceptible host.

Rheumatoid arthritis. Although the cause of RA is unknown, it has been recognized that many different arthritogenic stimuli activate inflammatory responses in immunogenetically susceptible hosts. Thus, studies have focused on exogenous infectious agents, endogenous substances, such as connective tissue proteins (e.g., collagens and proteoglycans), and altered immunoglobulins as the causative candidates. The concept that RA is an infectious disease has been
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Many of these interindividual variables relate to severe underlying pathogenic mechanisms. Inflammatory conditions that may have common uncausality but rather associations between two chronic diseases. The main focus of our attention is directed not towards current information, we do not propose that periodontitis can be explained by genetic factors. While the HLA-DR phenotype is not particularly strong for periodontitis, there is a report indicating that it is an important component of the genetic susceptibility to some forms of this disease. In addition, polymorphisms in the interleukin-1β (IL-1β) gene cluster have been shown to have a significant correlation with some forms of periodontitis in certain populations. Are Bacteria a Common Etiologic Link Between Periodontitis and Rheumatoid Arthritis? There are a number of shared features between microorganisms that can induce RA in a genetically susceptible host and the recognized periodontal pathogens. Nonetheless, RA is still not largely recognized as a disease resulting solely from bacterial challenge. On the other hand, technological and conceptual advances have permitted the identification of bacteria or groups of bacteria associated with specific periodontal diseases. Close inspection of the virulence factors of periodontal pathogens would suggest that such a response could be feasible. Thus, the possibility that ongoing periodontitis could trigger RA in genetically susceptible individuals is plausible. Notwithstanding the above, these concepts remain speculative until the causative agent for RA can be definitively identified. To date, no infectious agents have been identified as the cause of RA in humans. Indeed, current information does not support the concept that a single antigen is responsible for synovial inflammation. It is possible that there is no single primary cause of RA and that different mechanisms may independently lead to synovial inflammation in susceptible individuals. It is important to recognize that, based on current information, we do not propose that periodontal pathogens cause, or are associated with, RA. The main focus of our attention is directed not towards causality but rather associations between two chronic inflammatory conditions that may have common underlying pathogenic mechanisms.

Immunogenetics

Periodontitis. It has been reported that more than 50% of the variance in several features of chronic periodontitis can be explained by genetic factors. Many of these interindividual variables relate to severity of periodontal destruction, and other inflammatory responses are attributed partly to the amount and type of cytokines that individuals produce. While the HLA-DR phenotype is not particularly strong for periodontitis, there is a report indicating that it is an important component of the genetic susceptibility to some forms of this disease. In addition, polymorphisms in the interleukin-1β (IL-1β) gene cluster have been shown to have a significant correlation with some forms of periodontitis in certain populations. For RA, the strongest genetic associations are found within the HLA genes. Using DNA sequencing and molecular-based typing, it has been demonstrated that the disease-conferring portion of the D region is confined to a short sequence within the third hyper-variable region of HLA-DRB1 gene which includes the amino acid positions 67 through 74. The HLA genes and gender constitute about 30% of the genetic risk in RA, while other genetic factors such as cytokine genes, germline genes, and T-cell receptors also account for some of the genetic predisposition to RA. Effector Mechanisms of Tissue Destruction in Rheumatoid Arthritis and Periodontitis There is almost universal acceptance that a variety of cytokines and matrix metalloproteinases (MMPs) are upregulated and intimately involved in the pathogenesis of both periodontitis and RA; many of these effector molecules appear to be common to both diseases. The task now is to identify the specific cytokines, their concentrations, the cells they affect in vivo, the stages in which they are active, and the role and concentrations of their inhibitors. While the effects of cytokines on normal cellular processes are important, it is their purported roles in pathophysiology that may result from excessive production, dysregulation, or inadequate inhibition that have gained most attention. Very simply, cytokines can be classified into functional groups based on the cells of origin, and all major types have been identified and located in inflamed synovial and periodontal tissues.

Periodontitis has very similar cytokine profiles to RA, consisting of persistent high levels of proinflammatory cytokines, including IL-1β and tumor necrosis factor-alpha (TNF-α), and low levels of cytokines which suppress the immunoinflammatory response such as IL-10 and transforming growth factor-β (TGF-β). These cytokines, together with low levels of tissue inhibitors of metalloproteinases (TIMPs) and high levels of MMPs and prostaglandin E2 (PGE2), are associated with the active stages of periodontitis. The destruction of soft and hard tissues seen in RA is also the result of not only a large number of cytokines...
but also the sustained presence of other effector molecules released by resident and migrating cells. Together, these soluble mediators of inflammation are able to induce degradation of collagen and proteoglycans either through direct or indirect means. Production of the arachidonic acid metabolite PGE₂ as well as the release of neutrophil-associated enzymes, such as neutrophil elastase and β-glucuronidase, together with the secretion of matrix metalloproteinases by macrophages and synoviocytes, all contribute significantly to the pathogenesis of RA.

Formulation of the Hypothesis
On the basis of the above considerable similarities between the pathological and clinical features of RA and periodontitis (especially in the advanced and aggressive forms of these diseases), we have proposed that in some susceptible individuals, there are common features of an underlying and presently unknown dysregulation of the inflammatory mechanism which predisposes these individuals to advanced, aggressive, and severe forms of either disease.

Studies on Relationships Between Periodontitis and Rheumatoid Arthritis
To date, very few studies have examined the association between RA and periodontal disease, and the results have often been conflicting. For example, Finnish studies found no correlation between periodontal disease and arthritis, while others suggested a higher prevalence of periodontal bone loss in RA. A major reason for these discrepancies relates to the lack of uniformity in classifying the various forms of periodontal disease and RA. Indeed most of the early studies failed to take into account the various forms of RA and periodontal disease and, as a result, grouped all subjects as either having RA or periodontal disease with little or no regard for subclassification for more detailed analyses. In light of these limitations, it is clear there is a need to re-examine the extent of the association between specific types of RA and periodontal disease. In particular, it is our thesis that the more aggressive or severe forms of periodontal disease and RA will show a very close correlation in terms of coexistence.

In our first pilot study, investigating self-reported disease experience, the prevalence of moderate to severe periodontitis was significantly elevated in individuals with RA (unadjusted relative risk of 4.7). In addition, the converse was also true in that periodontitis patients had a higher prevalence of RA compared to the general population (unadjusted relative risk of 1.5).

In a subsequent study, 65 patients attending a rheumatology clinic were studied for their level of periodontitis and RA. A control group consisted of age- and gender-matched individuals who did not have RA. No differences were noted for the plaque and bleeding indices between the control and RA groups. The RA group did, however, have significantly more missing teeth than the control group and a greater percentage of these subjects had deeper pocketing compared to the controls. The percentage of alveolar bone loss correlated positively with the principal parameters of RA severity.

These two pilot studies have resulted in several significant findings. Contrary to current dogma, RA patients do not have impaired oral hygiene (judged by plaque and bleeding scores). Perhaps more importantly, it was noted that individuals with severe RA are more likely to have advanced periodontitis and vice versa. Although many RA patients take medications that can reduce periodontal destruction (i.e., NSAIDs and immunosuppressants), we have noted significant periodontal destruction in these patients. This indicates that prior to the development of RA symptoms, the periodontitis was most likely developing and not detected. Thus, disease duration may be a very important factor. Finally, in order to understand the interrelationships between periodontitis and RA, it is necessary to categorize the disease on the basis of severity and duration (i.e., type of disease).

Recently, using an animal model, additional evidence has been presented to indicate a significant relationship between periodontitis and rheumatoid arthritis. From this study it was reported that inducing experimental arthritis in the rat (adjuvant arthritis) resulted in periodontal breakdown characterized by alveolar bone loss and increased matrix metalloproteinase activity in adjacent gingival tissues. Interestingly, all of these reactions occurred without manipulating the oral or subgingival microflora.

Osteoclast Activation and Vascular Damage – A Common Pathway in Periodontitis and Rheumatoid Arthritis?
Most recently, studies from our laboratory (unpublished data) have begun to investigate the codistribution of cytokines involved in vascular damage and bone resorption in biopsies from graded rheumatoid arthritis and periodontitis lesions. Since the tumor necrosis factor (TNF)-like molecules and their receptors have been shown to be involved in both processes, we have chosen to study the receptor activator of nF-kappa B ligand (RANKL), osteoprotegerin (OPG), and TNF-related apoptosis inducing ligand (TRAIL) to determine at least one molecular mechanism common to both conditions.

The cell surface TNF-like molecule, RANKL and its receptor, RANK have been shown to be key factors regulating osteoclast formation and activation. It has been shown that when RANKL binds to RANK on the surface of osteoclast precursors, these cells...
differentiate to form mature osteoclasts. It is now clear that RANKL, together with macrophage-colony stimulating factor (M-CSF), is required for osteoclast formation. The soluble TNF "receptor-like" molecule, OPG, is a natural inhibitor of RANKL. OPG binds to RANKL and prevents its ligation to RANK. The importance of these molecules in regulating bone metabolism has been demonstrated by transgenic and gene knock-out studies in mice. Since these factors control physiologic osteoclast formation, it is reasonable to propose that they may also be key regulators of pathological bone resorption. Although RANKL is normally provided by osteoblast-like cells in bone, there are reports suggesting that lymphocytes present in rheumatoid tissues may be the main source of RANKL in inflammatory arthritis. Furthermore, CD3+ T cells from the human rheumatoid joint express RANKL and can promote osteoclast formation from rodent spleen precursors. In addition to lymphocyte production of RANKL, inhibition of RANKL by OPG treatment in vivo reduces both bone and cartilage destruction in a model of adjuvant arthritis.

Under certain conditions, human osteoclasts are derived from osteoclast precursor cells present in or near to the tissues of arthritic joints. More recent reports in humans and animals show that RANK/RANKL interactions may be required for osteoclast formation and bone resorption in the RA joint. Accordingly, we have recently demonstrated that OPG and RANKL are expressed in biopsies of inflamed rheumatoid synovium and periodontitis lesions. In addition, we have found (unpublished data) that another ligand for OPG, TRAIL, is expressed in the inflamed tissues of arthritic joints. OPG has been reported to be required for endothelial cell survival and growth. In addition, OPG knock-out mice have been shown to develop arterial calcification near to the tissues of arthritic joints. More recent binding studies confirm that OPG binds to TRAIL, although with less affinity than RANKL, in vitro and blocks its activity (unpublished data). The final piece of compelling evidence for the role of OPG in vascular damage comes from the fact that OPG knock-out mice develop vascular calcification. It is significant to note that calcification cannot be reversed by systemic treatment with recombinant OPG postpartum. This supports our concept that OPG must be expressed within the endothelial cells, either in an appropriate form or associated with other molecules, and this only occurs following normal synthesis within the healthy endothelial cells.

In light of the above, we propose that at least one underlying common molecular pathway in common between rheumatoid arthritis and periodontitis may lie within the RANK/OPG/TRAIL axis whereby OPG decreases with inflammation, RANKL increases with inflammation, and TRAIL increases with inflammation. These findings may be of considerable significance in light of OPG's ability to block the activity of TRAIL (and vice versa) and TRAIL's anti-inflammatory properties.

The production of OPG by endothelial cells may be significant for reasons other than its effects on bone metabolism, and there is now evidence to suggest that OPG might also regulate endothelial cell function. OPG has been reported to be required for endothelial cell survival and growth. In addition, OPG knock-out mice have been shown to develop arterial calcification as well as severe osteoporosis, suggesting that vascular endothelial expression of OPG may have a role in vascular homeostasis. One of the most unexpected findings from our recent studies of diseased periodontal and synovial tissues was the observation that endothelial cells produce large amounts of OPG (unpublished observations).

In response to proinflammatory cytokines TNF-α and IL-1β, OPG mRNA expression was dramatically enhanced, resulting in secretion of newly synthesized OPG and a reduction in cell-associated OPG. Such findings are consistent with our observations in vivo for active RA and periodontitis lesions. Vascular damage due to apoptosis is thought to precede vascular calcification and contribute to atherosclerosis. In addition, diabetic endothelial cell dysfunction is associated with DNA damage induced by poly (ADP-ribose) polymerase activation. The exact cause of endothelial cell dysfunction is not known but it is possible that molecules such as TRAIL, expressed in nearby cells and tissues, may be important. Our recent binding studies confirm that OPG binds to TRAIL, although with less affinity than RANKL, in vitro, and blocks its activity (unpublished data). The final piece of compelling evidence for the role of OPG in vascular damage comes from the fact that OPG knock-out mice develop vascular calcification. It is significant to note that calcification cannot be reversed by systemic treatment with recombinant OPG postpartum. This supports our concept that OPG must be expressed within the endothelial cells, either in an appropriate form or associated with other molecules, and this only occurs following normal synthesis within the healthy endothelial cells.

**COMMON PATHOGENESIS – COMMON TREATMENT?**

**Current and Emerging Therapies**

Currently, the mainstream “first-line” modes of treatment for RA remain the NSAIDs such as aspirin, naproxen, diclofenac, and ibuprofen. Their mechanism of action through the inhibition of cyclooxygenase (COX) synthesis produces both analgesic and antipyretic properties. While these medications are effective in reducing the pain symptoms in RA, they do not significantly alter its course.

The use of NSAIDs for management of periodontal disease has been studied over the past 20 years. While the results appear promising, the widespread clinical use of these medications to alter the course of periodontitis has not been universal. One particular problem with their use for the management of periodontitis appears to be a “rebound” effect following cessation of the medication.
With the discovery of two COX enzymes responsible for PGE2 production, designated COX-1 (constitutively expressed) and COX-2 (inducible), a variety of COX-2 inhibitors have been studied for their potential to stop or slow down bone resorption. One of the first COX-2 inhibitors developed, tenidap, has been shown to inhibit not only cyclooxygenase and PGE2 production but also IL-1, IL-6, and TNF-α production. To date, COX-2 inhibitors have not been thoroughly studied for their potential to modify bone resorption in periodontitis.

In contrast to the NSAIDS, which do not significantly alter the course of RA, a newer family of medications designated disease-modifying anti-rheumatic drugs (DMARDs) has been developed. To be classified as a DMARD, the medication must demonstrate an ability to change the course of RA for at least 1 year as evidenced by sustained improvement in function, decreased synovitis, and prevention of further joint damage. Examples of these medications include parenteral gold salts, methotrexate, sulfasalazine, hydroxychloroquine (antimalarial drug), penicillamine, azathioprine, and leflunomide. A major drawback in the use of DMARDs is their considerable toxicity.

Another emerging area of potential for host modification in periodontitis and rheumatoid arthritis is control of the MMPs that are important mediators of connective tissue breakdown in both hard and soft tissues. In this regard, tetracyclines and various chemical analogues have been found to inhibit MMP activity by a mechanism that is independent of their antimicrobial property. A number of clinical trials using low-dose tetracycline to modify periodontitis have been carried out, with the most recent data indicating that low-dose doxycycline is safe and significantly effective. Nonetheless, it is still recommended that these data be interpreted with caution to differentiate between statistically significant and clinically relevant findings. The role of MMP inhibitors in managing RA has been less well studied but promising results are emerging. In particular, a recent study has demonstrated that low-dose and antimicrobial (higher) dose doxycycline, when used adjunctively with methotrexate, produces enhanced improvements in global scores of RA severity in humans than methotrexate combined with placebo.

Control of cytokines and their receptors is also emerging as a field of considerable promise. For example, blocking the IL-1 receptor and using gene therapy to deliver IL-1 receptor antagonist are two strategies under investigation to modulate the effect of elevated IL-1 in inflamed tissues. Similarly, other studies have shown that blocking the activity of another important inflammatory cytokine, TNF-α, has therapeutic efficacy in RA patients. The roles of IL-1 and TNF antagonists in a primate model of periodontitis have demonstrated a reduction in the inflammatory infiltrate in close proximity to bone as well as reduction in the formation of osteoclasts and reduced bone loss.

Clearly, many of these biologic agents, which target specific molecular events associated with acute and chronic inflammation, have significant potential to alter clinical outcomes for both RA and periodontal disease. With the emerging understanding that RA and periodontitis are multifactorial diseases, combination therapies that target multiple disease outcomes are also emerging. For example, in an animal study, it was reported that the administration of a combination of a chemically modified tetracycline (CMT-1) plus an NSAID, such as flurbiprofen or tenidap, synergistically inhibited severe bone destruction in arthritic rats, with the suppression of MMP activity in the joints. Similar encouraging results have been reported for periodontitis in humans.

Notwithstanding the above, it must be recognized that periodontitis differs in one significant way from RA through our understanding that the subgingival biofilm is a key etiologic factor. Unlike periodontal disease, no specific bacterial etiology has been identified for RA. Thus, while host modification of disease processes are possible for periodontitis, controlling the bacteria that cause periodontal infections remains a significant focus for periodontal treatment and prevention. At best, host modification can be only an adjunct treatment for periodontitis. However, until an etiologic factor can be found for RA, host modification remains the mainstay of treatment.

CONCLUSIONS

There is no question that periodontitis and RA have many pathologic features in common. Emerging evidence suggests a strong relationship between the extent and severity of periodontal disease and RA. While this relationship is unlikely to be causal, it is clear that individuals with advanced RA are more likely to experience more significant periodontal problems compared to their non-RA counterparts, and vice versa. Hence, the possibility exists that both conditions result from a common underlying dysregulation of the host inflammatory response. The precise nature of this dysregulation remains to be established.

There is accruing evidence to support the notion that both conditions manifest as a result of an imbalance between proinflammatory and anti-inflammatory cytokines. As a result, new treatment strategies will emerge for both diseases that may target the inhibition
of proinflammatory cytokines and destructive pro-
teases.

Through a better understanding of these two com-
mon chronic inflammatory conditions, it is hoped that
areas of similarity can be exploited to determine the
true relationship between these diseases and com-
mon areas of treatment. Already, it can be predicted
that the periodontal status of patients with RA should
be carefully screened.

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