**ABSTRACT:**

Two most common chronic inflammatory diseases affecting mankind are rheumatoid arthritis and periodontitis. Etiology of the two may differ but have similarities in their pathogenesis, immune response, diagnosis and treatment. Over the past decade, research exploring the binary connection are numerous and growing by the day. This article enumerates the association between the two and with special significance to the role of periodontal pathogens like *P. gingivalis* on citrullination in the pathogenesis of rheumatoid arthritis.

**Key words:** Rheumatoid Arthritis, Periodontitis, Citrullination, Cytokines, Heat shock proteins

**INTRODUCTION**

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. Rheumatoid arthritis can also cause inflammation of the tissue around the joints, as well as in other organs in the body. Because it can affect multiple other organs of the body, it is referred to as a systemic illness and is sometimes called rheumatoid disease. While rheumatoid arthritis is a chronic illness, meaning it can last for years, patients may experience long periods without symptoms. However, RA is typically a progressive illness that has the potential to cause joint destruction and functional disability.

The classic characteristics of this disease are bilateral and symmetric chronic inflammation of the synovium (synovitis). In addition to the typical pattern of inflammation, patients with RA may experience systemic manifestations such as fatigue, loss of appetite, weakness and vague musculoskeletal pain. Also, patients with rheumatoid arthritis have an increased risk of premature mortality which is proportional to the severity of the course of the disease.

Rheumatoid arthritis and other rheumatic conditions involving chronic joint symptoms affect 42.7 million people, costing $65 billion per year in the United States. The disease is three times more common in women than in men and has a peak incidence of onset in the fourth and fifth decades of life. Rheumatoid arthritis affects all ages, races, and social and ethnic groups. The disease can begin at any age and even affects children (juvenile rheumatoid arthritis). The prevalence of rheumatoid arthritis in the adult Indian population is 0.75%, which projected to the whole population, would give a total of about seven million patients in India.

Periodontal disease is one of the most chronic disorders of infectious origin with a prevalence rate of 10-60% in adults depending on the diagnostic criteria. PD has been proposed as having an etiologic or modulating role in cardiovascular and
cerebrovascular disease, diabetes, and respiratory disease and adverse pregnancy outcomes. In the past decade, growing body of evidence shows an association between rheumatoid arthritis and periodontitis. There is cross susceptibility between these two diseases and remarkable similarities in the pathogenesis, inflammatory host response governed by immunogenetics, thus providing useful insights into these diseases.

The aim of this article is to discuss the epidemiological, pathological and immunological relationships between the two chronic inflammatory diseases affecting humans and the evolving common and economical therapeutic management strategies emerging from these links.

**Progression of RA and Periodontitis**

RA is characterized by inflammation of the synovial membranes and cartilage and bone resorption. Periodontitis is characterized by loss of connective tissues within the periodontium and destruction of (alveolar) bone support. Although there are fundamental differences in the etiology and anatomical involvement of periodontitis and RA, similar patterns of disease progression in RA and periodontitis can be seen (Table 1).

**Table 1. Patterns of disease progression in RA and periodontitis**

<table>
<thead>
<tr>
<th>RHEUMATOID ARTHRITIS</th>
<th>PERIODONTITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-limited RA</strong></td>
<td><strong>Well-maintained periodontitis</strong></td>
</tr>
<tr>
<td>Disease commences, but does not progress to cause significant damage</td>
<td>Disease commences, but with simple treatment it can be controlled such that little or no further progression occurs</td>
</tr>
<tr>
<td><strong>Easily controlled RA</strong></td>
<td><strong>Downhill periodontitis</strong></td>
</tr>
<tr>
<td>Disease becomes established, but can be controlled with &quot;first-line&quot; Medications</td>
<td>Disease becomes established and with a mixture of simple and complex therapies it can be largely controlled, although some slight ongoing destruction over time may be noted</td>
</tr>
<tr>
<td><strong>Progressive RA</strong></td>
<td><strong>Extreme downhill periodontitis</strong></td>
</tr>
<tr>
<td>Disease becomes established and continues to progress. Use of second line medications may be of little help in arresting disease progression</td>
<td>Disease becomes established and despite simple and complex therapies continues to progress and cause further tissue damage and tooth loss</td>
</tr>
</tbody>
</table>

**Association studies between rheumatoid arthritis and periodontitis**

It has been reported that patients with longstanding active RA have a significantly increased incidence of PD when compared with healthy subjects and that patients with PD have a higher prevalence of RA than patients without PD. de Pablo and colleagues, using data from the Third National Health and Nutrition Examination Survey (NHANES III), showed a significant association between RA and PD in the US population. A recent study evaluated patients with RA for the prevalence and severity of PD and their relationship to RA disease activity and severity with patients with osteoarthritis (OA) serving as controls. PD was more common and severe in patients with RA when compared with patients with OA.

**Periodontal microbiota and rheumatoid arthritis**

Several research groups have reported an increased variety and number of oral bacterial DNA and antibodies targeting these bacteria in serum and synovial fluid of patients with RA. *P. gingivalis* antibody levels have been shown to correlate with anti-CCP (anti-cyclic citrullinated peptide) antibody...
levels, making this periodontopathic oral bacterium an attractive candidate environmental trigger in the development of RA. Bacterial antibody (IgG) levels of *P. gingivalis*, *P. intermedia*, *P. melaninogenica*, and *B. forsythus* were found to be significantly higher in RA patients when compared with those of the controls, which could be important to the etiopathogenesis of RA.\(^9\)

*P. gingivalis* is currently the only known bacterium with expression of peptidyl arginine deiminase (PAD), which represents an important pathogenic factor of RA. The PAD expressed by *P. gingivalis* is not entirely homologue to human PAD but leads to an irreversible, post-translational conversion of arginine to citrulline. It has been proposed that oral citrullination of human and bacterial proteins by *P. gingivalis* PAD (PPAD) in an infectious context prior to the onset of RA could break tolerance and trigger a latent antibody response against citrullinated protein.\(^12\) Once tolerance is breached, citrullination of host proteins by human PADs perpetuates the immune response through epitope spreading and cross-reactivity, resulting in chronic inflammatory disease (Figure 1).

Another best established auto antigen detected in synovial tissue of RA patients is citrullinated α-enolase. A sequence of nine amino acids (Asp-Ser-Arg-Gly-Asn-Pro-Thr-Val-Glu) spanning the immunodominant epitope on the citrullinated enolase peptide-1 (CEP-1) is 100% identical to the corresponding region in *P. gingivalis* enolase, and affinity-purified antibodies to CEP-1 react with recombinant enolase citrullinated *in vitro* from both humans and *P. gingivalis*,\(^13\) providing an attractive target for molecular mimicry between human and bacterial species.

**Periodontitis, rheumatoid arthritis, and genetic factors**

The relationship between human leukocyte antigens (HLA) determinants and periodontitis is well studied. Examination of the DRB1*04 alleles that code HLA-DR4 in patients with RPP, showed a significantly higher frequency (42%) of one of the DRB1 subtypes than the control group (7%).\(^14\) These DRB1 subtypes are part of the so-called shared epitope genotypes, which also play a role in other inflammatory diseases like RA. Hitchon and colleagues\(^16\) reported an association between immune responses to the oral pathogen *P. gingivalis* and the presence of ACPA in a population with a high background prevalence of RA-predisposing HLA-DRB1 alleles. This gene-environment interaction may result in breaking self-tolerance to citrullinated antigens or amplification of these autoimmune responses or both and may ultimately lead to the development of RA.

**Superantigens in RA & Periodontitis**

Superantigens are proteins that bind simultaneously to V beta (V\(\beta\)V) chain of the T-cell receptors (TCRs) and \(\alpha\) chain of the major histocompatibility complex II molecules. They induce T cell activation and proliferation by binding the TCR and MHC II simultaneously. TCRs of the V\(\beta\) gene (V\(\beta\) 6, 8, 14, and 17) are more frequent in patients with RA than in the control groups.\(^17\) These superantigens of RA can be influenced by oral bacteria, although the *P. intermedia* stimulates the expression of V\(\beta\) 8 and V\(\beta\) 17 genes in CD4 (+) T cells, and both bacteria *P. gingivalis* and *P. intermedia* can also increase the expression of V\(\beta\) 6 and V\(\beta\) 8.\(^18\)
Heat shock proteins in RA & Periodontitis

Heat shock proteins form an ancient, primary system for “intracellular self-defense”. Heat shock proteins are present in cells under normal conditions, but are expressed at high levels when exposed to a sudden temperature jump or other stress. Heat shock proteins stabilize proteins and are involved in the folding of denatured proteins. Presence of Seventy-kilodalton *Prevotella melaninogenica* HSP and *P. intermedia* HSP is established in periodontal disease. However, HSP 70 antibodies are also found in the synovium of patients with RA and occur in the synovialis if the HSP 70 expression is triggered by specific stress factors and pro inflammatory cytokines.19

Cytokines and MMP’s in rheumatoid arthritis and Periodontitis

The role of the T helper 17 (Th 17) cells in the host defense is not completely known. It is shown that IL-17 stimulates the generation and mobilization of neutrophils and is instrumental in the defense of extracellular bacteria. Th 17 cells and IL-17 play an important role in the pathogenesis of RA. Also, Th 17 cells are also present in chronic periodontal disease,20 contributing to the etiopathogenesis of periodontal disease.

IL-1 cytokines are key mediators of immune responses, inflammation and tissue destruction in both RA and periodontitis. IL-1β levels are elevated in synovial fluids from RA patients21 and IL-1β is produced by synovial tissue macrophages, activated T cells, fibroblasts and chondrocytes. IL-1β is also prominent in periodontal tissue and gingival crevicular fluid of patients with periodontitis and is stimulated in a variety of resident and immune cells by components of oral bacteria (e.g. LPS).22 Excessive IL-1β in both disorders accounts for increased local blood flow, neutrophil infiltration and activation of connective tissue turnover via stimulation of MMP secretion from osteoclasts, fibroblasts and neutrophils.

IL-18 is present in the synovial membranes of patients with RA and is thought to amplify the inflammatory response by promoting the release of other cytokines, in particular TNF-a, granulocyte—macrophage colony stimulating factor (GM-CSF) and IFN-g. IL-18 has also been shown to promote angiogenesis, prevent endothelial cell and fibroblast apoptosis and modulate various cell lineages, including keratinocytes, osteoblasts, osteoclasts and chondrocytes, in RA.23 Measurements of IL-18 in periodontal tissue and in the circulation indicate that IL-18 is associated with active periodontitis24 although there are, as yet, no direct functional data linking this cytokine with destructive processes in periodontitis.

IL-33, in its intracellular form, is highly expressed within endothelial cells in the RA synovium, suggesting a pathogenic role.25 Increased microvasculature is a prominent histological finding in periodontitis, so it would be interesting to investigate expression of IL-33 associated with endothelial cells in periodontal tissue.

Biyiköðlu et al26 compared gingival crevicular fluid (GCF) levels of matrix metalloproteinase (MMP)-8 and -13 and tissue inhibitor of MMP (TIMP)-1 in patients with rheumatoid arthritis (RA) and systemically healthy counterparts with inflammatory periodontal disease. They found lower total amounts of MMP-8 in the healthy control group than in RA-gingivitis, RA-periodontitis, and healthy-periodontitis groups. MMP-13 levels were similar in all five study groups. This study indicates that the simultaneous appearance of RA and PD has no influence on the investigated parameters.

CONCLUSION

It is clear that there is evidence for the relationship between the presence of periodontal disease and the development of rheumatoid arthritis. Both share some common therapeutic strategies like the use of non steroidal inflammatory drugs, tetracyclines and anti cytokine agents. Use of inhibitors to adhesion molecules and disruption of cell signaling pathways have shown promising results in the arthritis model and are to be tried in periodontitis. Citrullination by periodontopathic bacteria have opened up a new channel for development of novel therapeutic agents. Therefore, inhibition of bacterial and human PAdS could become the first treatment targeting the generation of the actual antigens that affect both the diseases.
REFERENCE


25. Carriere V, Roussel L, Ortega N et al. IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor invivo. Proc Natl Acad Sci USA 2007; 104:282-287.