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Rheumatoid Arthritis and Periodontal Disease

Apoorva B. Badiger and Triveni M. Gowda

Abstract

Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease (IMID), chronic progressive causing inflammation in the joints and resulting in painful deformity and immobility, especially in the fingers, wrists, feet, and ankles. Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or their groups, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, clinical attachment loss, or both. Individuals manifesting both periodontitis and RA may suffer from a unifying underlying systemic dysregulation of the inflammatory response. In the past few years, increasing attention has been given to aspects of oral health in patients with rheumatoid arthritis, especially related to associations with periodontal disease. In this chapter we will be reviewing about the pathophysiology of RA and role of inflammation, periodontal disease: a gateway to RA, oral manifestations of RA, immunogenetics of RA and periodontitis, treatment implications for RA and periodontitis based on common pathophysiology.

Keywords: Rheumatoid arthritis, periodontal pathogens, periodontitis

1. Introduction

The global RA prevalence estimate was 0.46%. Women are affected 2 to 3 times more often than men. Onset may be at any age, most often between 35 years to 50 years, but can also be during childhood. Several risk factors like smoking, genetic association, recovery from bacterial or viral infections, sedentary lifestyles have been associated with the development of RA. In India, an estimated prevalence rate of RA is 0.5%–0.75% [1]. The Surgeon General's report on *Oral Health in America*, published in 2000, documented the significance of dental health on the overall general health and well-being of a patient. Research findings indicate possible relationships between chronic oral infections, such as periodontitis, and systemic disorders, such as diabetes, cardiovascular and lung diseases, stroke, osteoporosis, and rheumatoid arthritis [2]. A recent meta-analysis revealed an increased risk of RA in patients with periodontitis. The cross-sectional study was conducted to assess the impact of periodontitis (PD) on the health-related quality of life (HRQoL) and oral health-related QoL (OHRQoL) of subjects with rheumatoid arthritis (RA) and PD and found that the interaction effect of both diseases significantly conferred impacts on their OHRQoL and HRQoL [3]. Snyderman and McCarty reported common inflammatory mechanisms are shared by RA and periodontal disease (PD). Periodontitis is an inflammatory disease affecting periodontium caused by specific microorganisms like *P. gingivalis* (Pg), *Aggregatibacter actinomycetemcomitans*

(Aa), *T. denticola*, *T. forsythia*. Interestingly, these bacteria are also noted in the serum and synovial fluid of the joints of RA patients [4]. Mainly Pg and Aa can indirectly cause inflammatory reactions in the body. A study was conducted by Paola et al. on 4461 participants, of whom 103 were classified as having RA. Participants with RA had more missing teeth when compared to non-RA patients. It was concluded that there is a stronger association between periodontitis and tooth loss with RA [5].

2. Pathophysiology of RA & role of inflammation

RA is one of the more common autoimmune disorders, affecting approximately 1% of the population worldwide, and is characterized by dysregulated inflammatory processes in the synovium of the joint eventually leading to the destruction of both cartilaginous and bony elements of the joint, resulting in pain and disability. In a susceptible individual, the interface of environment and genes results in a loss of tolerance of self-proteins that contain a citrulline residue. The recognition of antibodies is directed against citrullinated peptides in RA. Enzymes like peptidyl-arginine deiminases (PADs) cause citrullination to occur. Citrullination is a normal process, vital for normal skin formation and other physiologic functions. But, in RA an autoimmune response develops against citrullinated peptides detected as anti-citrullinated peptide antibodies (ACPA). One of the tests to detect these antibodies detects anti-cyclic citrullinated peptides (anti-CCP). The presence of anti-CCP is >98% specific for the diagnosis of RA; though not all patients with RA will develop anti-CCP antibodies [6].

In the synovial fluid of patients with RA, a significant increase of T cells bearing the CD4+, 4B4+ helper-inducer receptor phenotype, and a significant decrease in CD4+, 2H4+ suppressor-inducer receptor phenotype was found in the peripheral blood of RA patients. The predominant feature is inflammation, mainly in the synovium. The synovial membrane in RA becomes hyperplastic. There is an amplified amount of synoviocytes and are infiltrated with immune and inflammatory cells, particularly macrophages, B- and T-lymphocytes, plasma cells, and dendritic cells. Increased levels of cytokines play a vital role in the dissemination of synovial inflammation.

There is a rising interest in the associations between oral health and autoimmune and inflammatory diseases. Several epidemiologic studies have described associations between rheumatoid arthritis and periodontal disease. Recent clinical studies are increasingly linked with biological assessments to better understand the nature of these relationships. These elicit the body to create antibodies – known as autoantibodies that include rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) in turn produces tumor necrosis factor-alpha (TNF- α), Interleukin (IL)-1, IL-6, IL-8, transforming growth factor-beta (TGF- β), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) that damage the body's cartilage, bone, tendons, and ligaments, resulting in the symptoms of RA [7].

3. Periodontal disease: a gateway to RA

In the case of rheumatoid arthritis, the initiating factor is an autoimmune response to structural components of the joint; in periodontitis, the initiating factor is the subgingival biofilm. In both cases, the destructive inflammatory events are remarkably similar, although the pathogenesis varies as a result of the

different anatomy. There has been a longstanding association described between periodontal disease with RA, However, it is now recognized that a specific species of bacteria, esp. *P. gingivalis*, colonizes patients with periodontal disease and marks the progression from gingivitis to aggressive periodontitis that can cause citrullination of proteins the posttranslational modification leading to the production of anticitrullinated protein/peptide antibodies, the most sensitive and specific rheumatoid arthritis biomarker. This gets converted to a citrullinated peptide in presence of the Peptidylarginine deiminase enzyme in turn forming immune complexes activating complement system releasing various inflammatory mediators causing joint destruction [3]. High levels of citrullinated proteins at the infection sites of *P. gingivalis* and their presence and serum levels correlate strongly with disease severity.

Concerning underlying pathophysiology, Chronic Periodontitis and RA share many pathological features and release several mediators that are common to both conditions(interleukin 1-beta and prostaglandin E2). Likewise, collagenase that specifically degrades collagen, activity is greater in GCF of periodontitis patients than healthy controls, also is elevated in RA synovial fluid, gingival crevicular fluid (GCF), and gingival tissue. A systematic review demonstrated that disease activity of RA relates with serum levels of IL-6, TNF alpha, and C Reactive Protein may influence an increase in inflammation leading to bleeding on probing (BOP). Antibodies to cyclic citrullinated peptides are connected with more aggressive and erosive rheumatoid disease [5]. Persistent periodontal disease as a trigger for chronic arthritis in vulnerable individuals via dysregulation in oral microbiota and host immune barriers. This prespective indicates that RA could be a consistent risk factor for chronic periodontitis, in contrary, newer theories emphasize that periodontal disease is a risk factor for RA (**Figure 1**) [1].

Though osteoclast precursors (OCPs) are produced in the bone marrow, circulate in the blood and enter active bone resorptive sites, and differentiate to osteoclasts. Periodontal bacteria-induced systemic IL-6 drives the expansion of OCPs that traffic to sites of bone resorption to boost osteoclastogenesis in response to locally produced RANKL, signifying changes in the bone marrow that link periodontitis to other disorders of bone loss, such as rheumatoid arthritis.

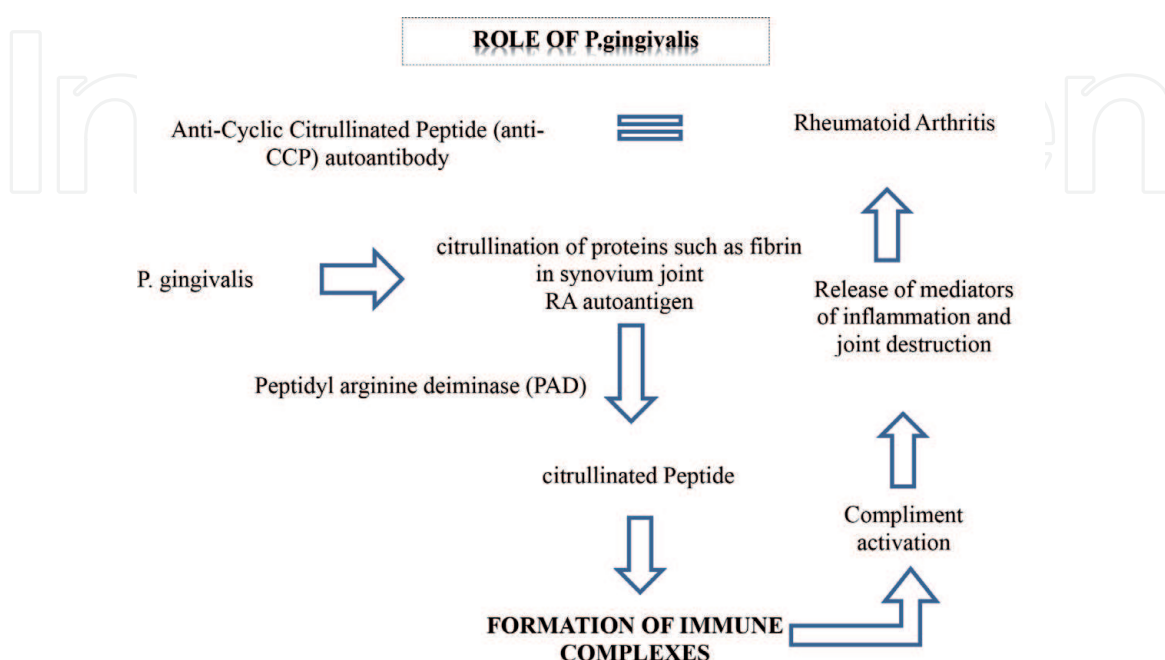


Figure 1.
 Role of *P.gingivalis* in pathophysiology of RA.

Periodontal disease yields an excess of citrullinated protein, that causes a break of tolerance with anti-CCP stimulation. *A. actinomycetemcomitans* induces citrullination in neutrophils by neutrophil extracellular trap (NET) activation and release through leukotoxin A. *P. gingivalis*, which has a specific deiminase enzyme, that could be most liable (Dr. Marotte) Also, research demonstrates it will be critical to address periodontal disease at its initial stage perhaps when it is associated with anti-CCP in preclinical RA, improved oral care and possible vaccination are probable treatment options. Targeting periodontal disease in RA patients or after the effects of anti-CCP is too late to make any changes for the individual. Rituximab and tocilizumab, two medications used to treat RA, also reduce the gingival inflammation and gingival bone destruction in periodontitis cases. However, infliximab enhances gingival inflammation while preventing periodontal bone loss [2].

Systematic review and meta-analysis revealed significantly increased risk of periodontitis in people with RA compared to healthy controls with a significantly raised mean probing depth, risk of bleeding on probing (BOP), and clinical attachment loss. Also, a study reported the presence of *P. gingivalis* and periodontal disease can be a trigger in individuals at risk for developing rheumatoid arthritis. Phase 1 therapy (scaling and root planing) has been effective as a therapy for established rheumatoid arthritis. Periodontal disease could also have probable downstream effects that impact additional related diseases [3, 8].

4. Oral manifestations of RA

The clinical manifestations of periodontal destruction is a result of the complex interplay among etiologic agents like bacterial plaque. Usually, it can be controlled by the body's defense mechanisms without destruction; however, when dysbiosis happens (like increased susceptibility, high bacterial load, or pathogenic infections/systemic infections) periodontal destruction could occur. Also, the recent outbreak of coronavirus infection throughout the world is a matter of global emergency. Patients with comorbidities, in their old age, and with a compromised immune system are at the highest risk of mortality.

Patients with autoimmune diseases, like lupus and rheumatoid arthritis (RA), already have a compromised immune system which is coupled with the prescribed immunosuppressive agents they take—making them more susceptible to infections. Rheumatoid arthritis has been associated with different oral manifestations, such as temporomandibular joint disorders, xerostomia, secondary Sjögren's syndrome, and periodontal disease (PD) [9].

5. Immunogenetics of RA and periodontitis

RA has various features typical of a complex genetic disease, such as multiple gene involvement, genetic variance, and incomplete penetrance. Susceptibility to rheumatoid arthritis (RA) is associated with defined HLA-DRB1 alleles. This specific regulation of DRB1 gene expression in RA patients represents one of the molecular mechanisms involved in the interrelation of HLA DRB1 genes. RA has several features typical of a complex genetic disease, such as genetic variance, incomplete penetrance, and multiple gene involvement. To date, the HLA complex is a strongly associated genetic factor for RA. DNA sequencing demonstrated that the actual disease-conferring portion of the D region of the HLA-DRB1 gene [10].

Various periodontal pathogens are involved in the process of periodontitis. Biofilm of periodontal disease supplies abundant Lipopolysaccharide (LPS).

Local production of IgA and IgM rheumatoid factor (RF) in periodontal disease has been documented. In particular, the HLA antigens A9, A28, BW15, and DR4 are associated with early-onset forms of periodontitis. The severity of RA and periodontal disease are partially due to intrinsic differences in the monocyte/T cell response traits. In both diseases, antigenic challenge (e.g. LPS) to the monocytic/lymphocytic axis would result in the secretion of catabolic cytokines and inflammatory mediators that would dominate. Also, IL-1 Genetic polymorphisms of cytokines have been associated with the susceptibility, severity, and clinical outcomes of inflammatory diseases, such as periodontitis and chronic arthritis [11].

6. Treatment implications for RA and periodontitis based on common pathophysiology

Many systemic conditions can alter the host's susceptibility to periodontitis. For instance, immunosuppressive subjects unable to mount an effective host response to subgingival microorganisms, thereby causing accelerated periodontal destruction. Contrarily, individuals with a substantial rise in the proinflammatory mediators may respond to periodontal pathogens with a boisterous inflammatory reaction causing periodontal tissue destruction. Though the interrelation of many systemic disorders on the periodontium is well documented, evidence suggests that periodontal infection may significantly increase the risk for various systemic diseases or may modify the natural course of systemic conditions.

Reports of the American Dental Association (ADA), American Academy of Oral Medicine (AAOM), British Society for Antimicrobial Chemotherapy (BSAC) American Academy of Orthopedic Surgeons (AAOS), suggest that routine antibiotic prophylaxis before dental treatment is not indicated for most patients with prosthetic joint replacement. However, antibiotic prophylaxis is indicated for almost all patients within the first 2 years after joint replacement patients, rheumatoid arthritis, systemic lupus erythematosus, etc. Many researchers cogitate patients with severe periodontal disease or other dental infections to be at great risk, and antibiotic prophylaxis may be indicated before dental treatment [2].

Several treatment approaches have been introduced to aim the host response to LPS-mediated tissue destruction. Either topically/systemic or in combination with scaling and root planing or surgical therapy. Pharmacologic inhibitors of NF- κ B and sp38 MAPK pathways are actively being developed to manage rheumatoid arthritis and inflammatory bone diseases and they have been applied in periodontal disease models with noteworthy accomplishments. MMP inhibits the signal transduction pathways involved in inflammation. With the use of this novel strategy, inflammatory mediators including pro-inflammatory cytokines (e.g., IL-1, TNF, IL-6), MMPs, and others would be inhibited at the level of the cell-signaling pathways required for the transcription factor activation [12].

NSAIDs such as aspirin, naproxen, diclofenac and ibuprofen are the first line of treatment for RA. Also, the use of NSAIDs in managing periodontal disease has been extensively studied and the results are promising. Disease-modifying anti-rheumatic drugs (DMARDs) are second-line drugs used in RA. Effects of administration of systemic gold salts were associated with significantly less periodontal destruction. Chemically modified antibiotics and genetically engineered proteins (monoclonal antibodies and pro-inflammatory cytokines correct the imbalance between the pro-inflammatory and anti-inflammatory cytokines involved in the pathogenesis of RA and periodontitis. Tenidap inhibits cyclooxygenase and PGE₂ production with inhibition of IL-1, IL-6, and TNF- α production

that reduces bone resorption and cartilage degradation as activating collagenase and stromelysin in RA patients [2].

Tetracyclines like Doxycycline have been advocated for treatment of patients with systemic diseases such as diabetes, rheumatoid arthritis that has led to improvements in the periodontal health and enhance reattachment or stimulate new attachment of the supporting apparatus and osseous formation. In the future, HMTs will likely be developed as adjunctive treatments for periodontitis. Novel *anti-cytokine drugs* developed for the management of rheumatoid arthritis, a disease with pathophysiology similar to that of periodontitis. Cytokines like TNF- α have been targeted by TNF- α antagonists mainly infliximab, etanercept which are effective in treating rheumatoid arthritis [12].

Rheumatic diseases cause patients to seek care for musculoskeletal pain or dysfunction or other problems. Temporomandibular Joint (TMJ) involvement follows the course of most joint involvement. Adherence to articular surfaces, capsular scarring, and shrinkage may further reduce joint mobility. NSAIDs are routinely used. Education, rest, and physiotherapy complete the regimen for treatment. A study by Kononen et al. reported that the subjective symptoms and the clinical signs of CranioMandibular Disorders (CMD) in RA, Psoriatic Arthritis (PA), and Ankylosing spondylitis (AS) are caused mainly by the respective general joint diseases, which directly affect the masticatory system, especially the TMJ. Further, signs and symptoms of CMD are more frequent and severe in RA than in PA or AS [13].

7. Conclusion

RA, being a common autoimmune disease, is associated with inflammation of the joint and, if left untreated, results in joint destruction and resultant disability. Periodontal disease is an infectious process that necessitates bacterial presence and host response that is affected and modified by local, environmental, systemic, and genetic factors. Both RA and periodontitis have remarkably similar pathology. Numerous studies documented interrelationships between them. Individuals suffering from RA more likely to experience significant periodontal problems compared to non-RA patients. With this understanding that the imbalance between pro and anti-inflammatory cytokines in the pathogenesis of RA and periodontitis, emerging therapies have focused on the inhibition of destructive proteases and pro-inflammatory cytokines. These therapies hold tremendous promise in altering the course of progressive forms of RA and periodontitis. Closer attention to oral health in these patients will improve quality of life by providing insights for treatment and prevention.

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