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REVIEW ARTICLE

# Impact of Oral Health on Rheumatoid Arthritis

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## ABSTRACT

This is a narrative review describing how oral infections and diseases associate with rheumatoid arthritis. From the voluminous oral microbiom, bacteria can get access to circulation through inflamed periodontal tissue, oral mucosa, and carious teeth. This results in upregulation of a number of chemokines and cytokines that often cause chronic, subclinical systemic inflammation with consequent organ pathology. The periodontal pathogen Porphyromonas gingivalis was observed to cause citrullination of proteins that play a role in the development of arthritis by generating of specific autoantibodies such as anti-citrullinated peptide antibody. These migrate and form immune complexes at the synovial membrane of joints. In general, patients with rheumatoid arthritis should have a healthy mouth. Dry mouth is a symptom seen among many patients with rheumatic diseases, also rheumatoid arthritis. Because saliva is one of the principal defense factors of the mouth, hyposalivation renders the patient liable to oral diseases. Consequently, the patients must drink enough daily and use saliva substitutes when necessary, and, above all, maintain good oral hygiene daily. In rheumatoid arthritis, manual dexterity may be impaired, however, causing cleaning the teeth difficult. Hence, patients with rheumatic diseases like rheumatoid arthritis need counseling and individual oral health care instructions by oral health care professionals for implementation at home. An electric toothbrush should be recommended. Regular oral health examinations by dentists are needed more often than among the healthy.

**Keywords:** Rheumatoid arthritis; Oral health; Dry mouth; Periodontitis; Porphyromonas gingivalis; ACPA.

## Introduction

Sir William Osler stated already at the end of 19th century: "The health of the mouth is the window to the health of the body". Hundred years later, an association has indeed been found between poor oral health and many systemic diseases like the rheumatic diseases[1]. This connection has particularly been observed in patients with Sjögren´s syndrome[2,3]. However, in many rheumatic diseases, hyposalivation and xerostomia are presenting symptoms with consequent problems of oral health[4]. Because saliva is one of the principal defense factors of the oral cavity, low salivary output affects dental and mucosal health. Thus, the patients with rheumatic diseases suffer from dry mouth, i.e., xerostomia. In particular, dental caries and periodontal disease can be problems in such patients. The worst cases are those with Sjögren´s syndrome, or patients who have received radiotherapy to the head and neck[5,6].

Recent research has also found an association between periodontal disease and rheumatoid arthritis (RA). The periodontal pathogen *Porphyromonas gingivalis* has been specifically associated with the development of joint pathology by exerting anti-citrullinated peptide antibody (ACPA) generation[7,8].

In this narrative review, we outline the current knowledge on the association between oral health and RA in adults. We mainly leave out other rheumatic diseases like Sjögren´s syndrome and oral mucosal problems as seen in lichen because there is voluminous literature available elsewhere on these rheumatic-associated diseases. Our principal aim in the present article is to point out how oral infections may increase human inflammatory burden in general. Further, oral diseases may even be a trigger for autoimmune diseases, such as RA. Oral infections may further reduce the effect of antirheumatic medication.

## Hyposalivation and Xerostomia

Oral discomfort including dry mouth is characteristic to patients with rheumatic diseases, such as RA, when compared with healthy controls. For example, in a study by our group on a random sample of 1500 members of the Finnish Rheumatism Association, 19.6% of the patients with rheumatic diseases *vs.* 2.9% of healthy controls reported symptoms of severe dry mouth[9]. Apart from Sjögrens´syndrome where hyposalivation is a presenting symptom, in another Finnish study subjective dry mouth (xerostomia) was reported by 8% of patients with mixed connective tissue disease, 46% of those with RA, and 44%, respectively, of patients with ankylosing spondylitis[4]. Because saliva is one of the principal defense factors of the mouth, patients with hyposalivation are particularly prone to oral and dental diseases[10].

## Oral Diseases

Oral diseases are highly prevalent in populations. Recent World Health Organization data show that approximately 50% of world population suffer from one or other form of oral disease[11]. Gingivitis and periodontitis are the most common chronic inflammatory diseases worldwide in adults[12]. Dental caries affects 2.3 billion people globally, while 50% of populations suffer from periodontal disease. Oral cancer is one of the 10 most common cancers, with an estimated 300-700 thousand new cases every year.

These alarming figures emphasize the importance of maintaining good oral health daily because both caries and periodontal diseases are fully preventable. Unfortunately, both at the individual and population level, this is not the case. Thus, poor oral health, which leads to chronic infection and inflammation, is detrimental to health in general. The high prevalence oral diseases explain why these diseases are often seen to associate with several systemic diseases like rheumatic diseases.

*DENTAL CARIES*

Rheumatoid arthritis with the subsequent hyposalivation and immunosuppressive medication used in the treatment renders the patients liable to caries. Caries is caused by oral bacteria that ferment dietary carbohydrates to acids, which dissolve the dental hard tissues enamel and dentine resulting in cavities. Tooth destruction then may lead to dental pulp infection with potential spread to the alveolar bone and further. However, literature is sparse regarding the specific effects of rheumatic diseases on caries. Most studies published on the area are cross-sectional with low numbers of patients.

Martinez-Martinez et al.[13] investigated 80 RA patients and 80 controls and observed that the patients had more caries cavities, 5.8 vs. 3.9, respectively. Further, the caries-inducing bacteria, like *Streptococcus mutans* counts were higher among the patients indicating an increased risk for caries. Nevertheless, a Spanish study on 73 RA patients and 73 controls found that the patients had poorer oral hygiene levels compared with controls, but difference was not observed in caries prevalence[14]. Earlier, a study from our group from Finland on 77 patients with different rheumatic diseases and their controls, observed only slightly worse dental health in the patients[4]. Later, we observed in another patient material with 53 newly diagnosed RA patients, 28 patients with chronic RA, and 43 controls, respectively, that patients with high activity of RA had statistically significantly increased dental caries prevalence[15].

*PERIODONTAL DISEASE*

Without appropriate treatment, gingivitis could progress to periodontitis, which destructs alveolar bone leading to loss of teeth. Inflammatory biomarkers from inflamed periodontal tissue include mediators such as interleukin (IL)-1β, -6, -8, -18, tumor necrosis factor (TNF)-α, matrix metalloproteinase (MMP)-8 and -9, tissue inhibitors of metalloproteinase (TIMP)-1[16,17] . Jørgensen et al.[18] reported from pro-inflammatory cytokines, such as interleukin (IL)-1α, IL-1β, IL-1 receptor antagonist, IL-4, IL-10, TNF-α, and soluble tumor necrosis factor receptor I (TNF receptor I), which may be presented rather late in the pathogenesis of RA. However, immunoglobulin M (IgM), rheumatoid factor (RF), immunoglobulin G (IgG) and ACPA may reflect the onset of RA even up to two decades earlier. According to the follow-up study by Äyräväinen et al.[19], patients with early, untreated RA had worse periodontal health compared with chronic RA patients. This might explain why the onset of RA could be triggered by periodontitis, the oral disease that induces systemic inflammation[20]. Patients with early or chronic RA suffered more frequently from moderate periodontitis when compared with population controls without RA[19]. Furthermore, tooth loss is more frequent

in patients with RA, which complicates eating and finally affects quality of life[21].

## The Role of *Porphyromonas gingivalis* in Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune inflammatory disease caused by a combination of risk factors, including genetic, hormonal, and environmental factors such as infections and smoking[22,23]. Interestingly, RA and infections by the periodontal pathogen *Porphyromonas gingivalis* have been observed to be linked together. The pathogenesis of RA is related to the citrullination process and autoimmunity. This process starts with massive activation of the innate immune response with an increase in antigen-presenting cells and B cell activation resulting in specific autoantibodies such as ACPA which migrate and form immune complexes at the synovial membrane of joints[24]. Human immune system recognizes structural proteins containing terminal arginines. In RA patients, the higher activity of deaminases (mainly peptidyl arginine deiminase) can transform arginine into citrulline. The immune system cannot recognize this, which leads to the formation of ACPA. These antibodies can be detected in RA patient years before their first articular symptoms[25,27]. The presence of autoantibodies, mainly ACPA, indeed are the autoimmune basis of RA.

Rheumatoid arthritis and infections by *P. gingivalis* might associate with the initiation and progression of the disease[28-35]. As said, *P. gingivalis* produces a specific peptidyl arginine deiminase, *P. gingivalis* peptidil-arginine deiminase[36]. It is possible, that this deaminase citrullinates human proteins and forms the ACPA. Furthermore, *P. gingivalis* peptidil-arginine deiminases may also citrullinate peptides released from *P. gingivalis* gingipain-mediated degradation of fibrinogen and alphaenolase[37]. Possibly, it may also promote self-citrullination[36,38,39]. *P. gingivalis* peptidil-arginine deiminase may thus trigger the onset of RA and its symptoms by forming an antigen that can disperse the immune tolerance of the host by increasing the release of ACPA[40,41]. According to study of Courbon et al.[35], *P. gingivalis*-induced periodontitis triggered seropositive ACPA in RA patients with systemic inflammation and increased bone erosion.

## Other Periodontal Bacteria and Rheumatoid Arthritis

There might be more periodontal bacteria with an ability to citrullinate proteins and induce the ACPA formation[42]. For example, the periodontal bacterium *Aggregatibacter actinomycetemcomitans* can induce hypercitrullination in host neutrophils probably mediated through pore-forming leukotoxin A. This leads to membrane degradation on neutrophils and ACPA formation. Furthermore, of other oral bacteria, *Tannerella forsythia*[43] as well as *Fusobacterium nucleatum* together with *P. gingivalis* may trigger ACPA in RA patients[44]. Hence, it is obvious that more studies are called for also in the context of oral microbiome and RA.

## Effects of Antirheumatic Medication

Effective treatment with disease modifying antirheumatic medication (DMARDs) within the first year of RA onset (window of opportunity[45]) is beneficial for preventing joint damage and disability[46-48]. Methotrexate (MTX) is suggested as the first treatment

strategy by The European League Against Rheumatism (EULAR) recommendations[49]. Leflunomide (LEF) has also been used with or without MTX. Conventional DMARDs (cDMARDs) usually contain hydroxychloroquine (HCQ) and sulfasalazine (SSZ) in various combinations with MTX. Further, glucocorticoids are used to suppress inflammation and to improve function in the affected joints. Modern antirheumatic medication also includes the use of biologic medication, bDMARDs. These drugs have specific targets: etanercept, certolizumab pegol, infliximab, adalimumab, and golimumab that neutralize TNF-α function, rituximab suppresses B-cell activity, abatacept inhibits T-cell co-stimulation, anakinra inhibits IL-1, and tocilizumab IL-6, respectively. Äyräväinen et al.[50] reported, however, that bDMARDs or cDMARDs had no remarkable influence on oral health. Further, the use of cDMARDs with early RA and bDMARDs with chronic RA slightly improved saliva secretion[15]. Tocilizumab has a beneficial effect on periodontal parameters according to the study by Kobayashi et al.[51]. Periodontal condition improved also in patients who used infliximab[52-54]. Periodontal parameters improved also with the use of etanercept or adalimumab[55,56]. Finally, even though MTX has been used in RA since 1980´s, surprisingly little information is available on its effect on periodontal disease. In general, however, more studies are called for to assess the role of antirheumatic medication on oral health and vice versa.

## Oral Health Maintenance

Even though only a few properly controlled clinical studies have been published on the area of oral diseases and rheumatoid arthritis on clinical basis it is clear that maintaining proper oral hygiene daily is often impaired due to problems with manual dexterity among the patients with rheumatic diseases; particularly so among the RA patients. Thus, the patients should have regular oral health care appointments to diagnose and treat oral health problems. Unfortunately, this does not seem to be the case. For example, the study by Pokrajac-Zirojevic et al.[57] showed that 45% of RA patients had not visited a dentist during the last two years. This, then, resulted in more tooth extractions when compared with controls (8.6 vs. 3.9). Consequently, regular oral examinations and individual oral hygiene instructions by dentists and dental hygienists are the keys of maintaining good oral health in patients with RA. Such a practice would be beneficial to the patients, and it should become routine in the primary oral health care clinics and hospitals. Namely, as Kreher et al.[10] recently reported, RA patients indeed have higher caries prevalence than non-RA controls. This may be partly the result of poor manual dexterity due to progressive disease. Reduced saliva secretion caused by RA is also challenging to the patient[14]. As regards periodontitis, Yamashita et al.[58] found in their study that in patients with RA periodontal inflammatory burden associated with the clinical response to bDMARDs. Similarly, Kobayashi et al.[59] recently reported how periodontitis follows the clinical response to bDMARDs.

## Conclusion

Patients with rheumatoid arthritis evidently suffer from more oral diseases than the healthy. Infections originating from the mouth can be detrimental particularly for patients

taking immunosuppressive medication. Some periodontal pathogens like *P. gingivalis* by causing citrullination of proteins may even trigger joint pathology. The patients often have difficulties in cleaning their teeth because of problems in manual dexterity. Dry mouth caused by the disease and its treatment further worsens the situation and affects the quality of life. Maintaining good oral hygiene daily calls for proper equipment for home care as well as products for prevention of the oral diseases. When compared with healthy subjects, patients with RA call for frequent check-ups and individual counseling by the oral health professionals.

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The authors have no conflicts of interest

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