

Critical oral diseases in rheumatoid arthritis: knowing, understanding and preventing

Lesões bucais importantes na artrite reumatoide: conhecer, compreender e prevenir

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Victória Boëchat Feyo

Dentistry Student

School of Dentistry – Universidade Federal de Juiz de Fora
Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora - MG
E-mail: victoria.feyo@odontologia.ufjf.br

Paula Karoline Fonseca

Dentistry Student

School of Dentistry – Universidade Federal de Juiz de Fora
Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora - MG
E-mail: paulinhakf@hotmail.com.br

Viviane Angelina de Souza

Ph.D. MD

Rheumatology Department, University Hospital - Universidade Federal de Juiz de Fora
Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora - MG
E-mail: vivi.reumato@gmail.com

Ariane Cezano de Oliveira Reis

DDS

School of Dentistry – Universidade Federal de Juiz de Fora
Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora - MG
E-mail: arianecezanoodonto@hotmail.com

Rafael de Oliveira Fraga

MD

Rheumatology Department, University Hospital - Universidade Federal de Juiz de Fora
Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora - MG
E-mail: rafaelfraga.jf@gmail.com

Maria das Graças Afonso Miranda Chaves

Ph.D., DDS

Dental Clinic Department, School of Dentistry – Universidade Federal de Juiz de Fora
Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora - MG
E-mail: duque05@gmail.com

Priscila de Faria Pinto

Ph.D.

Protein Structure and Function Study Laboratory, Department of Biochemistry, Institute of Biological Sciences – Universidade Federal de Juiz de Fora

Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora – MG
E-mail: priscila.faria@outlook.com

Gisele Maria Campos Fabri

Ph.D., DDS

Dental Clinic Department, School of Dentistry – Universidade Federal de Juiz de Fora
Campus Universitário, Rua José Lourenço Kelmer, s/n – São Pedro, Juiz de Fora - MG
E-mail: gisele.fabri@ufjf.edu.br

ABSTRACT

Rheumatoid Arthritis (RA) is a chronic multifactorial disease characterized by inflammation of the synovial membranes that line the joints and affect 1% of the world population. This narrative review aims to discuss a highlight mechanisms about the main oral manifestations in patients with rheumatoid arthritis researching epidemiological data. This narrative review was performed by searching the literature on the MEDLINE / PubMed databases for articles in English focused on oral diseases in patients with RA. Scientific studies show that RA patients are at high risk of developing oral changes, for example, periodontal disease (PD), Sjögren's syndrome (SS), xerostomia and temporomandibular joint disorder (TMD). There is a complex interrelation between oral diseases and RA, with sufficient scientific evidence to assure that there is an association that is bidirectional and impacts the pathogenesis and evolution of these conditions. This bidirectional connection with effects on the inflammatory profile of individuals reinforces the need for future clinical studies that confirm the effectiveness of prevention and early diagnosis protocols for rheumatological disease and the main associated oral diseases.

Keywords: dentistry, oral complication, salivary gland, rheumatoid arthritis.

RESUMO

A artrite reumatoide (AR) é uma doença multifatorial crônica caracterizada pela inflamação das membranas sinoviais que revestem as articulações e afeta 1% da população mundial. Esta revisão narrativa tem como objetivo discutir um mecanismo de destaque sobre as principais manifestações bucais em pacientes com artrite reumatoide pesquisando dados epidemiológicos. Esta revisão narrativa foi realizada por meio de busca na literatura nas bases de dados MEDLINE / PubMed de artigos em inglês com enfoque em doenças bucais em pacientes com AR. Estudos científicos mostram que pacientes com AR apresentam alto risco de desenvolver alterações orais, por exemplo, doença periodontal (DP), síndrome de Sjögren (SS), xerostomia e disfunção da articulação temporomandibular (DTM). Existe uma complexa inter-relação entre doenças bucais e AR, com evidências científicas suficientes para assegurar que existe uma associação que é bidirecional e impacta a patogênese e evolução dessas condições. Essa ligação bidirecional com efeitos no perfil inflamatório dos indivíduos reforça a necessidade de futuros estudos clínicos que confirmem a eficácia de protocolos de prevenção e diagnóstico precoce das doenças reumatológicas e das principais doenças bucais associadas.

Palavras-chave: odontologia, complicações bucais, glândula salivar, artrite reumatoide.

1 INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, destructive, and inflammatory disease, characterized by an autoimmune response that causes inflammation of the synovial membrane and can functionally compromise the affected joints ^{1,2}. The prevalence of rheumatoid arthritis is about 1% of the world population and the disease is three times more frequent in women ³.

In addition, the disease has as main characteristics symmetrical swelling of the joints, sensitivity to palpation, stiffness and severe impairment of movement in the involved joints ^{2,4}. Symptoms start with a small number of compromised joints, morning stiffness, nonspecific symptoms such as fatigue and a sensation of flu. Polyarthritides develops with disease progression ⁵. Due to the chronic nature of the disease, when uncontrolled, RA causes the patient's functional disability and, thus, reduces his quality of life ⁶.

RA treatment involves several pharmacological approaches and the choice of protocol depends on the patient's clinical status ^{2,5}. Medication currently used include glucocorticoids, non-steroidal anti-inflammatory drugs and disease-modifying drugs (DMARDs) of synthetic origin (conventional DMARDs, such as methotrexate or targeted DMARDs, as janus kinase inhibitors [JAK]) or biological origin (biological DMARDs), such as tumor necrosis factor [TNF] inhibitors, costimulation modifiers, drugs that destroy B cells and inhibitors of interleukin-6 ^{2,5,7}. These types of drugs work to reduce pain and inflammation and therefore improve the signs and symptoms of the disease ².

Several studies corroborate the idea that there is a relationship between rheumatoid arthritis and some oral manifestations. However, understand the scientific evidences about pathogenic mechanisms involved in this relationship is crucial to development of precise strategies of prevention and therapies of both conditions. So, the present study was performed looking for the highlights topics enrolled on mechanisms of illness due to an autoimmune disease and the participation of pathological alterations in the oral cavity. The purpose of this narrative review was then to discuss a highlight mechanisms about the main oral manifestations in patients with rheumatoid arthritis researching epidemiological data.

2 METHODOLOGY

This narrative review was performed by searching the literature on the MEDLINE / PubMed databases for articles in English language focused on oral diseases in patients

with Rheumatoid Arthritis. The search method involved an association of relevant keywords and titles in the medical field. The search terms used were “dental diseases”, “dentistry”, “oral complication” and “salivary gland”, “periodontal disease”, “gingivitis”, “pediatric rheumatic diseases”, “juvenile idiopathic arthritis”, “juvenile rheumatoid arthritis”, “Juvenile systemic lupus erythematosus”, “childhood-onset systemic lupus erythematosus” and “juvenile dermatomyositis”. The ranged from 2012 and 2020, considering systematic reviews, clinical studies and experimental studies with animals. All articles selected were full texts.

3 RESULTS/DISCUSSION

3.1 PECULIAR ASPECTS OF RHEUMATOID ARTHRITIS AND THE ORAL CAVITY

RA is a systemic inflammatory disease, predisposed to affect and destroy joints in the feet and hands, being it chronic and progressive. The etiology of RA is still uncertain^{8,9}. However, it is believed that an interaction between genetic and environmental factors contributes to the etiopathogenesis of this disease^{1,2,9}.

HLA genes and gender represent approximately 30% of the genetic risk of RA, while other genetic factors, such as genes encoding cytokines, T cell receptors and germline genes, also have an influence on the genetic predisposition of RA^{1,2}.

In addition to these genetic conditions, several environmental factors are associated with the pathogenesis of RA, such as viruses (parvovirus B19, Epstein-Barr), bacteria (streptococci, mycoplasmas, proteins and E. coli), cigars, hormones and silica¹.

Studies show the relationship between RA and oral manifestations resulting from systemic conditions that affect the immune response, being responsible for the variation in the susceptibility and severity of oral changes in these conditions^{2,10}.

3.2 PERIODONTAL DISEASE ASSOCIATED WITH RA: RELEVANCE AND IMPACTS

Periodontal disease is a chronic inflammatory condition that affects the supporting tissues (gums, periodontal ligament and alveolar bone), and is caused by the accumulation of dysbiotic microbial biofilm on the teeth surface².

RA patients are more susceptible to dysbiosis in the oral cavity since the disease itself and the resulting treatment unbalance the immune system^{6,9,11,12}. Anaerobic species such as *Atopobium*, *Leptotrichia*, *Lactobacillus salivarius*, *Prevotella* and *Cryptobacterium curtum* are in greater quantities in the microbiota of these patients, while

the genera *Corynebacterium* and *Streptococcus*, associated with health, are present in smaller quantities^{6,12}. A local inflammatory response then occurs, altering the expression of inflammatory mediators in the periodontal tissues, which favors the proliferation of facultative and anaerobic bacteria and gram-negative taxa¹².

Periodontal pathogens penetrate through the gingival margin towards the connective tissue and can generate constant and less intense bacteremia caused by tooth brushing or chewing. Thus, pathogens can colonize sites far from the body and generate other pathological processes. In the study by Molon (2019)² it was detected in the synovial fluid of patients with RA, the DNA of *Treponema denticola*, *P. gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Prevotella nigrescens* and *Fusobacterium nucleatum*. In addition, in the same study, elevated antibody titers against *T. forsythia*, *P. intermedia* and *P. gingivalis* were identified in the serum and synovial fluid of patients with RA. Other studies have shown a considerable increase in the number of periodontopathogenic bacteria in patients with RA, associated with worse periodontal state^{6,9,11,13}.

In addition, the pathogenesis of PD is associated with an increase in the production of inflammatory mediators such as TNF- α and IL-1 β , and a reduction in IL-4 that contributed to the onset and advancement of inflammation during chronic synovitis. Therefore, in both diseases there is imbalance between pro-inflammatory and anti-inflammatory cytokines in connective tissue and bone, which are responsible for tissue damage^{2,4,6,10,13,14,15}. Several other pathological and immunological similarities of the two diseases are observed, among them, an increase in inflammatory infiltrate, involving neutrophils, monocytes and T and B lymphocytes; reduced levels of anti-inflammatory mediators, such as IL-10². And, besides having genetic factors (HLA gene) and smoking as an etiological factor, PD and RA, they can also generate systemic inflammation, with increased levels of C-reactive protein in plasma².

Another important aspect about the interrelation between PD and RA is related to the peptidyl arginine deiminase (PAD) enzyme. It is known that the main event in the early stages of RA may be the activity of PAD, which transforms arginine into citrulline. Although protein citrullination is present not only in this disease, the formation of anti-citrullinated protein antibodies (ACPA) is almost exclusive in this situation^{2,6}. Although there is little evidence, Rodríguez-Lozano et al. (2019)⁶ stated that a gram-negative anaerobic bacterium, such as *Prophyromonas gingivalis*, upon releasing a specific deaminase, induces protein citrullination, which through an imitation process can

stimulate the formation of ACPA in patients with RA or susceptible to this disease. As a result, there is a cross reactivity of ACPAs generated periodontal with antigens present in the joint microenvironment that amplifies the immune response, further intensifying the inflammation associated with RA ^{2,6}.

Scientific evidence shows that patients with RA have more severe PD than those without RA; and patients with RA associated with periodontitis have more active rheumatoid disease ^{7,14,16}. However, the study by Mühlberg (2017)¹⁷ observed a different result on this association between PD and RA. In this research, the control group had higher prevalence of PD than the group of RA patients. This result, despite controversial, can be explained by an improvement in the periodontal condition of RA patients who received antirheumatic medication, due to the anti-inflammatory effects on periodontal tissue after a period of treatment ².

On the other hand, PD can affect the efficacy of the anti-tumor necrosis factor (anti-TNF) in patients with RA. Maintaining the gingival inflammatory condition can make it difficult to respond to treatment ^{15,18}.

3.3 XEROSTOMIA / HYPOSALIVATION IN RA PATIENTS: IMPORTANT SUBCLINICAL EFFECTS

Saliva plays an important role in maintaining homeostasis of the oral cavity. Xerostomia, or dry mouth sensation, is common in many groups of patients, such as the elderly, patients taking some medications, (e.g. antihypertensives), and in individuals with certain autoimmune diseases ^{14,19}. This condition is directly related to a higher incidence of oral diseases and also to complications in chewing, speech, taste and swallowing, in addition to interfering negatively in the physical, psychological and social functioning of the patient ^{1,7,16}. The prevalence of xerostomia indicates that more than 30% of patients have this complication ^{20,21,22}.

In addition, xerostomia is considered a cariogenic condition due to its relationship with hyposalivation and therefore the RA patient needs a follow-up with the Dentist during rheumatological treatment ¹⁹.

In this sense, RA may be associated with lymphocytic infiltration and destruction of exocrine glands ⁸, causing secondary Sjögren's syndrome (SS). The scientific literature demonstrates that patients with SS present significant reduction in the salivary flow and, as a result, have higher prevalence of dental caries, periodontal disease and early tooth

loss compared to the population without the syndrome, in addition to the quality of life related to their oral health patients is significantly reduced ^{7,14,23,24}.

3.4 TEMPOROMANDIBULAR JOINT IMPAIRMENT IN RHEUMATOID ARTHRITIS: UNDERSTANDING TO ACT

The temporomandibular joint (TMJ) plays an important role in crucial physiological processes, such as chewing, speaking and swallowing. Temporomandibular disorders (TMD) represents a group of inflammatory or degenerative diseases of the stomatognathic system involving TMJ and associated masticatory muscles ¹.

Due to the presence of synovial fluid, TMJ is easily affected by RA ²⁵. Patients with TMD associated with this disease report pain, swelling, impaired movement and crackling; moreover, in advanced stages, the individual may develop anterior open bite with preauricular tenderness or pain during movement, morning stiffness, malocclusion and decreased masticatory strength ^{1,25,26}.

Lin et al. (2017)²⁵ found that most patients with TMD associated with RA manifested symptoms before (18%) or after 1 year (30%) of the involvement of other joints in the body. On the other hand, regarding radiographic characteristics, Savtekin and Sehirli (2018)²⁶ stated that there may be no findings in the early stages, but in the late stages, the condylar joint surface is degenerated and the joint space is narrowed.

Regarding pharmacological therapy for RA, Lin et al. (2017)²⁵ showed that there was no significant reduction in the risk of TMD in patients treated with systemic glucocorticoids. However, those who used DMARD therapy with methotrexate, hydroxychloroquine or sulfasalazine were fully cured of TMD after 11 years of monitoring ^{1,25}.

This can be explained, since treatment with conventional DMARDs and biological drugs act on the immune system, making it difficult to bind pro-inflammatory cytokines to their receptors, which play an important role in the pathogenesis of RA, resulting in a rapid improvement in edema and joint pain ^{1,2,5,7}.

It is worth noting that, as the clinical manifestations of TMD are often silent, the patient's complaint is usually focused on the joints the are most affected by a systemic disease ^{27,28,29}. Thus, the clinician's focus on TMJ involvement becomes superficial when compared to other joints involved ^{28,29}. Therefore, it is important to understand the TMJ changes associated with RA, since TMD complaint can be an early manifestation of RA and its recognition helps in the early diagnosis of systemic disease ²⁵. In addition,

effective TMD control in RA patients requires specific therapy to control rheumatic condition activity ²⁸.

Table 1 shows the average incidence of the main oral diseases in patients with RA, according to epidemiological studies from the last 5 years. In figure 1 we summarize and compare oral complications in patients with RA.

Table 1 - Incidence of the main oral diseases in patients with RA

Oral diseases	Incidence (average±sd)	References
Periodontal disease	65±0,19	Rodríguez-Losano et al.(2019) ⁶ , Äyräväinen et al.(2017) ³⁰ , Choi et al. (2016) ³¹ , Eriksson et al. (2016) ³² , Huang et al. (2017) ³³ , Kim et al.(2018) ³⁴ , Kordtabar et al.(2019) ³⁵ , Lugonja et al.(2016) ³⁶ , Pons-Fuster et al.(2015) ³⁷ , Zhao et al.(2019) ³⁸ .
Xerostomia / Hyposalivation	25±0,17	Das et al.(2015) ²⁰ ,Brown et al.(2015) ³⁹ , Hamani et al.(2017) ²¹ , Harrold et al.(2020) ²² ,Hajiabbasi et al.(2016) ²³ , Sakr et al.(2018) ⁴⁰ , Santosh et al.(2017) ⁴¹ .
Temporomandibular Disorder	79±0,15	Cricoli et al.(2019) ¹ , Cordeiro et al.(2016) ²⁷ , Kurtoglu et al.(2016) ²⁸ ,González-Chaves et al.(2020) ⁴² , Mortazavi et al.(2018) ⁴³ .

In calculating the average, a total of 100 patients were considered.
sd= standard deviation.

Figure 1 - Oral complications in patients with RA

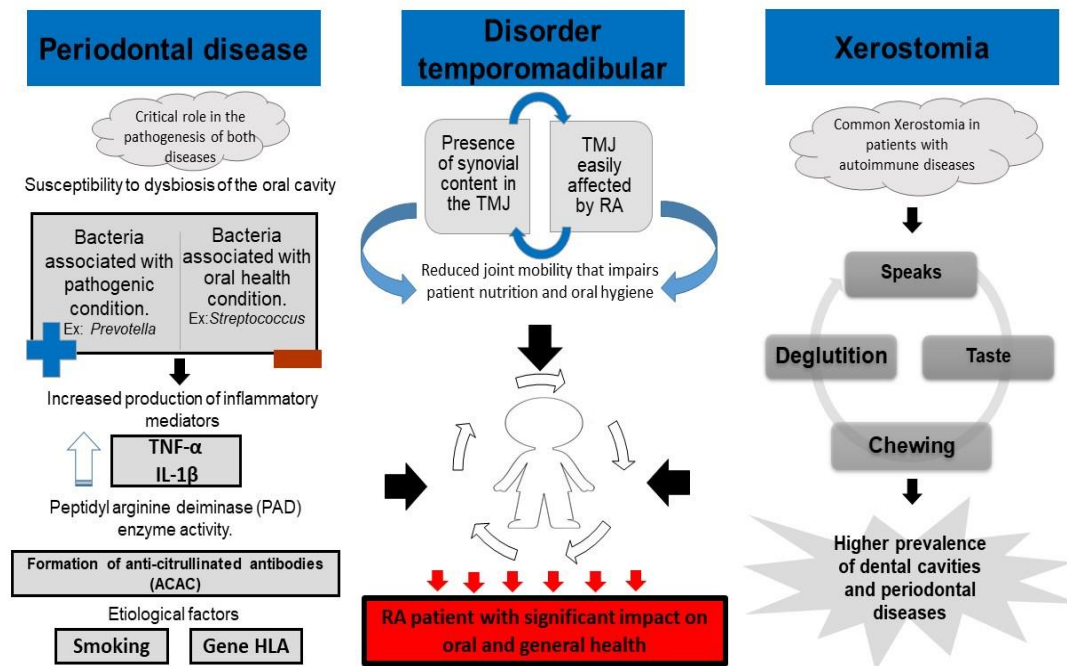


Figure 1. The figure shows the relationship between the main oral manifestations present in patients with rheumatoid arthritis. RA patients are more susceptible to dysbiosis in the oral cavity, which induces increased production of inflammatory mediators, formation of anti-citrullinated antibodies. In addition, PD and RA have the same risk factors - HLA gene and smoking. These changes have a local and systemic effect and trigger changes in connective tissue with notable clinical signs of periodontal disease and in the joints of patients with RA. Xerostomia is common in patients with autoimmune diseases, impairing speech, swallowing, taste and chewing. This reduction in salivary flow may be associated with a higher prevalence of dental caries and periodontal disease in these patients. In addition, due to its synovial content, ATM is easily affected by RA. This involvement generates a reduction in joint mobility of the TMJ, impairing function and impacting nutrition, oral hygiene and, consequently, oral and general health.

4 CONCLUSION

Understanding the pathophysiological mechanisms of oral diseases and RA contributes to a more effective approach and reduces possible complications and morbidity. Recognizing and understanding the main oral diseases that manifest in RA can favor the early diagnosis of RA, and, consequently, a better prognosis. However, knowing the mechanisms by which RA interferes with oral health is also essential and helps develop prevention strategies that can reduce the incidence of these manifestations and all their local and systemic repercussions. Thus, health professionals, working in interdisciplinarity, must know this interpellation to better care for and control RA.

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