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Relation between rheumatoid arthritis and periodontitis: Literature review

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Abstract
Autoimmune diseases affect 3 to 5% of the population, which the most common is rheumatoid arthritis (RA) in 27.6%. Many diseases including RA share pathogenic mechanisms and systemic cascades of inflammation, having an autoimmune disease significantly increases the risk of developing another disease. One of the risk factors for RA is periodontitis, *porphyromonas gingivalis* is a marker linked to determine the state of the disease. During inflammation takes place the citrullination of proteins and is produced under the action of the enzyme peptidyl arginine deiminase (PAD), this enzyme induces the citrullination of proteins and converts them into antigens recognized by certain specific antibodies to RA. PAD is expressed by inflammatory cells, and also by *porphyromonas gingivalis*, which is the only bacterium that expresses the PAD enzyme. In patients with RA the risk of periodontitis increases up to 13%. Some chronic and acute diseases are related to an aberrant expression of microRNA levels. To understand the disease caused by microRNA deregulation requires a specific expression in tissues that can recreate the individual function and mechanism of microRNA. They are critical regulators of host immunity and inflammatory response against pathogenic bacteria. The aim of this study is to conduct a literature review about the characteristics and risk factors of RA and the relation between periodontitis.

Keywords: Rheumatoid arthritis, periodontitis, microRNA

Introduction
Nowadays it has been found that 3 to 5% of global population has some autoimmune disease [1], rheumatoid arthritis (RA) being more frequently associated [2].
Autoimmune diseases are characterized by a slow and progressive advance, where the defense system loses the ability to recognize what belongs to the body, leading to the production of antibodies against the same cells, tissues or organs, being affected exocrine glands [3].
When a lymphocytic infiltrate is present in the salivary glands, the glandular parenchyma is affected and a decrease in salivary flow is manifested [4]. The normal volume of daily saliva is from 500 to 1000 ml [5], what it means 0.3 to 0.4 ml/min, however when values are found <1.5ml/15 min of stimulated total saliva, that is <0.1ml/min without stimulation [6], hyposalivation or hyposialia is presented, known by the decrease in salivary flow [7].
As there is a decrease in the salivary flow some alterations and diseases in oral cavity are presented, such as candidiasis, mucositis, angular cheilitis, aphthous ulcers, cervical and root caries, halitosis, gingival affection and periodontal disease it has been suggested [8].
Actually, a wide prevalence of periodontitis has now been found in RA, where *porphyromonas gingivalis* plays an important role in relation to the citrulized proteins of RA [9].
Periodontitis is a chronic inflammatory disease that gives as a result the loss of connective tissue and support bone. The reaction it is been determinate for the relation between bacteria and the host inflammatory immune response [10].
The aim of this study is to conduct a literature review about the characteristics and risk factors of RA and the relation between periodontitis.

Materials and methods
A review of literature was made including original articles, revisions of narrative and systematic literature in Pubmed and Google academic databases looking for the words "periodontitis", "rheumatoid arthritis".

Literature review

Autoimmune diseases

Autoimmune diseases affected between 3 to 5% of the population, being more common in women, and are associated with an increase in the morbidity and mortality rate; they are also in the tenth place of death causes in patients under 65 years [1].

Many autoimmune diseases, including RA, share pathogenic mechanisms and systemic cascades of inflammation, which significantly increase the risk of developing another autoimmune disease [2].

The immune system in charge of the body defense reacts against the body own tissues, which identifies them as foreign. In autoimmune disease, defense cells trigger inopportune and persistent inflammatory processes and therefore produce antibodies that are disoriented, known as autoantibodies, which react against the tissues themselves. These autoantibodies and inflammatory processes are responsible for the characteristics of autoimmune diseases[3].

There is currently a wide range of autoimmune diseases, the most common being RA in a 27.6%, lupus erythematosus in 7%, and Sjogren's syndrome in a 3.1% [1].

Rheumatoid arthritis

RA is a chronic, painful, disabling inflammatory disease that can lead to the extreme of functional disability if not treated properly. It is a multisystemic inflammatory disease that affects the synovial joints [4].

Antibodies and cytokines may develop many years before the diagnosis of RA. The clinical development of the disease occurs in phases: in the first phase it manifests itself as asymptomatic of generic risks, where environmental exposure occurs followed by a phase of immune activation. This phase is followed by a phase of active disease, where it begins with minimal joint symptoms and then turns out to be frankly arthritis. In early stages there are many cases in which it may not be classified according to the European League Against Rheumatism [5].

RA can be classified at establish criterias such as: 1) Evolution of the disease in inflammatory polyarthritis undifferentiated to the classic rheumatoid arthritis, which can take up to 5 years. 2) People genetically susceptible to exposure to environmental risk factors, this triggers the production of autoimmunity and antibodies, and these exposures can cause symptomatic inflammatory arthritis. Many spend a long time in the preclinical stage with development of antibodies; this is the time when risk factors can be modified to stop progression [5].

Rheumatoid arthritis risk factors

Within the pathological and non-pathological antecedents there are currently risk factors that contribute to the development of the disease, among them are some modifiable factors such smoking, periodontitis, vitamin D and infections [6].

a) Smoking

Smoking is the most studied and most easily preventable risk factor. In cases with passive smokers there is no increase in the risk of RA, however, it increases the risk for the generation of autoantibodies against citrulized proteins [6].

b) Periodontitis

It is a factor involved in the development of several immune diseases related to chronic inflammation. *Porphyromonas gingivalis* is a marker linked to determine the status of the disease [6]. Some studies have established the relationship between RA and periodontitis, where the role of citrullination, antibody response, and mediator release as a result of bacterial colonization has been proposed in the pathogenesis of RA [7].

There has been an increase in the prevalence of periodontitis and a high rate of tooth loss in patients with RA compared to the general population [5].

c) Vitamin D

Vitamin D deficiency is implicated in the pathogenesis of several autoimmune conditions. It performs immune and anti-inflammatory functions by differentiating T and B lymphocytes, dendritic cells and macrophages [8].

d) Infections

Some infections, particularly those with joint manifestations, such as Epstein Barr virus, parvo virus B19, chikungunya virus, and some bacteria are involved in the risks for RA because they act as direct triggers of joint inflammation [5].

Periodontal Disease

Periodontal diseases and conditions

Plaque induced gingivitis

Is an inflammatory response of gingival tissues presented by the action of plaque accumulation located below the gingival margin. Patients report some symptoms such as bleeding when brushing teeth, presence of blood in saliva, swollen and red gums, and halitosis. Clinical signs include erythema, edema, bleeding, tenderness and gingival enlargement. No indicators of loss of supporting structures are observed in radiographic analysis. Histopathological changes occur such as elongation of vessels in connective tissue, vasculitis of blood vessels adjacent to the junction epithelium, progressive destruction of collagen fibers, cytopathological alterations in fibroblasts and inflammatory infiltrate [9].

The molecular characteristics of the gingival transcriptome pattern have been evaluated during plaque induced gingivitis, because microRNA transcripts are not always translated into proteins, it is important to know which proteins are expressed and their relationship with the appearance of gingival inflammation and its associated risk factors [10].

In this section of periodontal diseases, plaque-induced gingivitis is modified by several factors and classified into:

A. Associated only with bacterial biofilm.
B. Potential modification factors of plaque-induced gingivitis. Among which are some systemic conditions such as systemic hormones that can be altered at puberty, during the menstrual cycle, in pregnancy and with the use of oral contraceptives, hyperglycemia, leukemia, smoking and malnutrition. Oral factors favoring plaque accumulation, such as prominent margins of subgingival restorations and hyposalivation, are also found.
C. Influence of medications on gingival enlargement.

Hyposalivation is an effect of medications that is frequently seen with the administration of antihistamines, decongestants, antidepressants, antihypertensives. Some of the effects of hyposalivation are the progression of cavities, taste disorders, halitosis, inflammation of the oral mucosa, gum and tongue, however, is also commonly associated with the presence of some diseases such as Sjogren's syndrome [10].

Non-plaque induced gingival diseases

Non-plaque induced gingival lesions usually occur as

manifestations of systemic conditions. The parameters included in this classification are genetic and developmental disorders, specific infections that may be of bacterial, viral or fungal origin; inflammatory and immune conditions and lesions, reactive processes, neoplasms, endocrine, nutritional and metabolic diseases; traumatic lesions and gingival pigmentations [11].

Periodontitis

According to the World Health Organization, within the group of oral diseases periodontitis is in sixth place, has a worldwide prevalence of affectation between 5 to 20% of the population, being caries the most common [12].

Periodontitis is a chronic inflammatory disease of multifactorial origin characterized by a progressive destruction of the tooth support apparatus. The main characteristics include loss of the supporting tissues, which translate into loss of clinical attachment, radiographically there is loss of alveolar bone, periodontal pockets and gingival bleeding [13].

It is a public health problem due to its high prevalence, in addition to the fact that it can lead to loss of teeth and disability, negatively affects both function and aesthetic, affecting the patient's quality life [13].

According to physiopathology have been divided into three forms of periodontitis:

1. Necrotizing periodontal diseases; including necrotizing gingivitis, necrotizing periodontitis and necrotizing stomatitis.
2. Periodontitis as manifestation of systemic diseases; classification of these condition should be based on the primary systemic disease, according with the codes of the International Statistical Classification of Diseases and Related Health Problems.
3. Periodontitis; its divided into stages, extent and distribution and grades.

a) Stages: based on severity and complexity of management where stage I is initial periodontitis, stage II moderate periodontitis, stage III severe periodontitis that has potential for tooth loss, and stage IV that has potential for loss the dentition.
b) Extent and distribution: can be localized, generalized and molar-incisor distribution.
c) Grades: correspond to the progression of the disease, A is slow rate of progression, grade B moderate rate, and C rapid rate [9].

Periodontal Affection in Rheumatoid Arthritis

The red complex of periodontopathogenic bacteria such as *porphyromonas gingivalis*, *tannerella forsythia* and *treponema dentícola*, play an important role in the progression of periodontitis. Increased levels of *porphyromonas gingivalis* contribute to the exacerbation of RA[7]. During inflammation the citrullination of peptides or proteins takes place, and produces under the action of the PAD enzyme [14], this enzyme induces the citrullination of proteins and converts them into antigens, recognized by antibodies against citrullinated cyclic antipeptide, these markers are specific to RA. PAD is expressed by inflammatory cells and also by *porphyromonas gingivalis*, which is the only bacterium that expresses the PAD enzyme [14].

According to one study it was found that 13% of patients with RA increase the risk of presenting periodontitis, where there is an increase in depth of probing and attachment loss [15]. However, a significant but poor association of the relationship between RA and periodontitis has been found, in which periodontitis contributes to the pathogenesis of RA, but studies stablishing the relationship are still required [16].

MicroRNA

MicroRNA (miRNA) are a form of small single-stranded RNAs, formed by 22 nucleotide base sequences that bind to approximately 60% of all genes. They are transcribed by DNA rather that translated into proteins, which regulate the functions of other genes in protein synthesis. These are genes that modulate other genes of codifying proteins. Even after considering thousands of new putative genes identified in the sequence of the human genome, as well as the genes that encode the transfer of RNAt and RNAr, about 95% of the genome is non-coding DNA. Sequence changes are often associated with a malfunction [17].

The human genome can encode more than 2500 miRNAs, which has emerged as one of the main negative regulators of gene expression [17]. MiRNA play a critical role in the development, secretion of proteins, and regulation of genes. To understand the disease caused by the deregulation of there miRNAs, specific tissue expression is required that can recreate the individual function and mechanism of miRNA *in vitro* and *in vivo*. They are critical regulators of host immunity and inflammatory response against pathogenic bacteria [18].

Increasing evidence indicates that miRNAs play a critical role in the early development of biological processes, cell differentiation, proliferation, apoptosis, rate of development and hematopoiesis, among other functions [19].

Altered miRNA expression is associated with numerous diseases. Some chronic and acute diseases are associated with aberrant expression of miRNA levels, which affect gene expression and cell functions during disease progression. For example, miRNA levels are found in imbalance in infectious diseases, genetic disorders, alterations in immune system function, insulin secretion, neurotransmitter synthesis, viral replication, chronic inflammatory diseases, cardiovascular diseases and many others [18].

MicroRNA and periodontal disease

MiRNAs have emerged as regulators of the immune response based on their ability to interfere with the post-transcriptional expression of multiple target genes [18].

Periodontitis is a chronic inflammatory disease of the periodontium that results in the loss of connective tissue and alveolar bone. It is well established that bacteria induce an inflammatory response that cause damage to periodontal tissues, and the severity of periodontal disease is something that depends on the dynamic balance and interactions between microorganisms and the host inflammatory response.

The local balance is tilted towards periodontal damage by excessive production of inflammatory cytosines and enzymes, such as interleukin (IL) 1 and 6; tumoral necrosis factor-a (TNF-a), prostaglandin E2 and metalloproteinase matrix. Other mediators such as miRNA may be involved in periodontal infection.

Most of the functions of miRNA are unknown, some of those involved in bone resorption by inflammation are hsa-miR-17 and hsa-miR-20a. This means that a target cell can be regulated by a group of miRNAs that share regulatory mechanisms and function as a biological network [20].

Conclusions

Rheumatoid arthritis is one of the most frequent autoimmune

disease, among the main risk factors is periodontitis, which is a factor involved in several autoimmune diseases related to chronic inflammation. There has been an increase in the prevalence of periodontitis and a high rate of tooth loss in patients with rheumatoid arthritis. In rheumatoid arthritis patients, the risk of periodontitis increases by 13%.

MicroRNA have a critical role in the development, secretion of proteins and regulation of genes. To understand the disease caused by the deregulation of these microRNAs requires a specific expression in tissues. Abnormal microRNA expression may result in rapid disease progression. MicroRNA expression of each individual disease are known, however, the relationship between the two diseases needs to be known.

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