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Periodontal Disease and Rheumatoid Arthritis: Exploring New Associations of Autoimmune Pathogenesis

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Abstract

Rheumatoid Arthritis (RA) and Periodontal Disease (PD) are chronic inflammatory diseases, partially resulting from the dysregulation of the host's inflammatory response. A growing number of clinical trials have demonstrated that there is a potential association between periodontitis and systemic rheumatic diseases, including RA in particular. However, the association between RA and susceptibility to periodontitis remains unclear, and the results obtained in individual studies are inconsistent and inconclusive [1]. Although the exact etiology of RA remains unknown so far, the production of pro-inflammatory cytokines and lymphocyte activation are crucial in disease events, just as they occur in periodontal disease [2-4]. However, many mechanisms in these diseases have not yet been sufficiently explored. Thus, our review study aims to create a current narrative review of the literature to address the pathogenic mechanisms of the association between periodontal disease and rheumatoid arthritis, for which we will use the requirements of "Scale for the Assessment of Narrative Review Articles" (SANRA) as the gold standard for writing the manuscript.

Objectives

A. Clarify new biochemical and microbiological processes involved in the association of rheumatoid arthritis and periodontal disease.

B. Validate treatment methods that involve the modulation of the host's immune response to inhibit the effects of rheumatoid arthritis and periodontal disease when they are associated.

Abbreviations: RA: Rheumatoid Arthritis; PD: Periodontal Disease; IBD: Inflammatory Bowel Disease; GCF: Gingival Crevicular Fluid; TNF: Tumor Necrosis Factor; PAD: Peptidyl Arginine Deaminase; PPAD: Porphyromonas gingivalis-Peptidyl Arginine Deaminase; MMPs: Matrix Metallo Proteinases; CD: Crohn's Disease; UC: Ulcerative Colitis; HPA: Hypothalamic-Pituitary-Adrenal; SFB: Segmented Filamentous Bacteria; SCFAs: Short-Chain Fatty Acids; DCs: Dendritic Cells; TLRs: Toll-Like Receptors; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; RF: Rheumatoid Factor; ACPA: Anti-Citrullinated Protein Antibodies; PDT: Photo Dynamic Therapy; BMD: Bone Mineral Density

Introduction

Many studies have found a link between Rheumatoid Arthritis (RA) and Periodontal Disease (PD), with both diseases sharing common pathogenic mechanisms. The pathogenesis promoted by both RA and PD are similar [5], both develop chronic inflammation and consequent tissue destruction, in addition to having the same risk factors and a

strong association epidemiological [6]. Regarding RA and its clinical diagnosis, we know that antibodies against citrullinated peptides are essential to define its diagnosis, although recent studies show that it is necessary to identify specific citrullinated antigens, as whole proteins, to explain the gaps in the pathogenic mechanisms. Some citrullinated antigens responsible for rheumatoid inflammation have already been discovered, such as type II collagen, vimentin, fibrinogen and alpha-enolase, which are found in the joints [7]. Antibodies against citrullinated fibrinogen and type II collagen are also known to cause inflammation via immune complexes in humans and animals [8].

Periodontitis, in which P. gingivalis is the main causative agent, is a chronic inflammatory disease of the supporting tissues of the teeth. P. gingivalis, one of the main initiating agents of periodontal diseases, can be found in 80-90% of patients with periodontitis and in 10-30% of healthy individuals [9,10]. The bacterium has recently attracted interest based on possible epidemiological links between RA and periodontitis [11] and the description of a new bacterial PAD [12] (hereafter referred to as PPAD), suggesting its potential etiological factor for P. gingivalis in RA diseases through its generation of citrullinated antigens, thus inducing the development of anticyclic peptide citrullinated (Anti-CCP antibodies) present in the pathogenesis of RA. After P. gingivalis was described as the only bacterium in the oral flora responsible for expressing the PAD enzyme, new studies were carried out solely on this microbiological model, delving into the explanation of the relationship between PD and RA, and other important biochemical mechanisms linking these two diseases, such as the host gut and its microbiome, have been little explored.

Periodontitis has been reported to be associated with Inflammatory Bowel Disease (IBD), and in a meta-analysis study by Yang-Yang She et al, 2020 with 599 patients, PD was shown to be significantly associated with IBD. Recent advances in the analysis of 16S ribosomal RNA from fecal bacteria show that dysbiosis, an imbalance of intestinal bacteria, is a common factor responsible for the occurrence of several autoimmune diseases, including RA. Other common factors may include the destruction of mucosal barriers in the gastrointestinal defense mechanisms and changes in substances produced by intestinal bacteria. After recent studies have shown that diseases with an autoimmunity character, such as RA and PD, are induced through "self" immune responses, this review aim is to explore a new axiomatic relationship between the imbalance of the intestinal microbiota and the appearance of RA and PD, clarifying the interrelationship of these two pathologies.

Periodontal Disease

Periodontal disease, which encompasses the group of gingivitis and periodontitis, is a frequent oral inflammation/infection that affects the supporting and supporting tissues of the teeth, the connective tissue and alveolar bone that supports the dentition [13]. The statistics of incidence and prevalence of cases of periodontal diseases vary due to bias, sites examined, uncalibrated examiner, erroneous classification of cases and number of teeth [14]. According to the 2016 Global Burden of Disease Study, periodontal disease was the 11th most prevalent condition in the world [14] with its prevalence fluctuating from 20% to 50% [15]. In addition, studies show that periodontal disease is associated with other common systemic conditions, such as diabetes, cardiovascular diseases, changes in the course of pregnancy, rheumatoid arthritis and chronic obstructive pulmonary disease [16,17].

The initial stage of this disease is classified as gingivitis, which is clinically characterized by gingival redness, swelling, bleeding, change in contour, loss of adaptation of the tissue to the tooth, and increased flow of Gingival Crevicular Fluid (GCF). The initial injury appears as an inflammatory response with the characteristic infiltrate of neutrophils. Bacterial chemotaxis of neutrophils causes degradation of vascular, epithelial, and tissue collagen, as well as activation of host systems, such as the complement system, kinins, and arachidonic acid pathways. In turn, periodontitis is clinically characterized by the loss of the periodontal ligament and the rupture of its attachment to the cementum, as well as the absorption of the alveolar bone. Studies show that the progression of periodontitis is a consequence of untreated gingivitis. It is widely accepted that from the beginning to its progression, periodontitis depends on the presence of microorganisms capable of causing the disease. Although more than 300 species of microorganisms have been isolated from periodontal pockets, studies show that only a small percentage of these pathogens are etiologic agents of disease. The dysbiosis that causes the change from periodontal health to PD is analogous to that of intestinal mucosal surfaces, in that a stable microbial community composed primarily of aerobic gram-positive bacteria changes to a pathogenic bacterial community characterized as microaerophilic and anaerobic gram-negative microorganisms. Three species of bacteria are strongly correlated with Parkinson's disease: *P. gingivalis, Treponema denticola*, and *Tannerella forsythia*, which represent the "red complex".

Rheumatoid Arthritis

The historical evidence of rheumatoid arthritis going back to records of rheumatic diseases in the Ebers Papyrus-which date back to 1500BC. In 400BC, the father of modern medicine, Hippocrates, also described arthritis, although at that time there was no differentiation between the various forms of arthritis. It was suggested that rheumatic disorders were the result of an imbalance of the four humors (from the Greek meaning 'juice' and rheum meaning 'current' or 'flow') and that these humors flow into the joint, causing the symptoms of rheumatic disease. Rheumatoid arthritis is an autoimmune disease that begins long before its clinical signs and symptoms appear. Over the years, the immune system of an individual can undergo changes, such as T cells and their interaction with the body itself. This is more susceptible in individuals with a genetic predisposition to the disease, but it is worth noting that the context and environmental exposures demonstrate great importance for the continuity of autoimmune processes. As well as the premature aging of the immune system of some individuals, causing a loss of telomeres that directly affects the development of T cells and neutrophils, in addition to the intestinal microbiota that may be the element of risk to trigger the evolution of the disease at the level of generating synovial inflammation, initiating the clinical symptoms of rheumatoid arthritis, which is already reported in the scientific literature, the intestinal microbiome can directly influence the inflammatory stages of an individual, this is due to the influence of metabolic potential on the innate and adaptive immune systems. The generated autoimmunity occurs due to post-translational protein modifications that can be citrullination and carbamylation. The latter is a process resulting from lysine enzyme-independent derivatization, while the former is related due to an enzyme-mediated removal of residual arginine. And on that basis, tissue inflammation, in addition to smoking, can increase the expression of the enzyme arginine deiminase.

MacGregor AJ, et al. 2000 in his study on monozygotic twins and genetic factors of rheumatoid arthritis showed that the heritability rate of the disease has an approximate value of 60%, demonstrating that there is a strong genetic potential, also demonstrating the need for environmental factors. In contrast, identical twins did not show a significant percentage of disease concordance, around 12% to 15%, suggesting that triggers such as smoking, dust inhalation and the microbiota, for example, provided by exposure to the environment are much more important in favor. the development of the disease. Research by Meng W, et al. Alabama 2017, demonstrates interference with DNA methylation in smokers with ACPA-positive RA, a difference that did not occur between groups of non-smokers.

A large study looking for differences between the DNA of healthy people and individuals with RA was carried out, and a distinct methylation pattern was identified in the HLA region of the genome. DNA methylation allows exogenous factors to interfere with cellular metabolic processes, as is the case of the study that showed that in smokers, where methylation levels were higher in patients with RA compared to non-smokers and carriers of the HLA risk allele -DRB1. Thus, it is possible to conclude that the interaction of genetic factors of people

susceptible to rheumatoid arthritis with exposure to environmental triggers converges to the development of the disease. The synovium is a physiologically thin mesenchymal membrane and when the inflammatory process begins, initiating the clinical picture of rheumatoid arthritis, there is a greater production of extracellular matrix, as well as the growth of fibroblasts. This culminates in a thickening of the membrane with abundant blood vascularization, in addition, the subintimal portion is colonized by inflammatory cells. Fibroblast growth produces intimal hyperplasia with blood vessels. With the chronification of the disease and the continuity of the autoimmune inflammatory process, the repair of the membrane-synovial tissue fails, in this way, the new cells are endowed with destructive characteristics, in addition to being proinflammatory factors.

With the great advance of studies on rheumatoid arthritis, the number of therapeutic resources has increased considerably in recent years. Based on currently available clinical and pharmacological data for rheumatoid arthritis treatment strategies, there is a focus on the chronic and final stage of the disease, being mostly nonsteroidal anti-inflammatory drugs, glucocorticoids, and activity-modifying drugs. rheumatoid arthritis (DMARD), which are of synthetic origin such as kinase enzyme inhibitors and methotrexate. There are also those of biological origin, which are: Tumor Necrosis Factor (TNF) inhibitors, costimulation modifiers, interleukin-6 and inhibitors of B cell depletion. Although there may be several ways to produce treatments due to the variety of pathological pathways of the disease, such as: genome stability, mitochondrial physiology, cell organelle biogenesis, cell endomembrane system, and skeletal cytology.

Association of Rheumatoid Arthritis and Periodontal Disease

A positive association between PD and RA has been theorized since Hippocrates described that extracting teeth could be a cure for arthritis in the 400s BC. Recently, the link between the two pathologies has been considered by several studies based on different populations from different continents [18]. Rheumatoid arthritis and chronic periodontitis are characterized as chronic inflammatory diseases caused by an exacerbated inflammatory reaction leading to destruction of connective tissue and bone. The association of chronic inflammation in both RA and PD reflects a predominant adaptive immune phenotype, the role of smoking, the imbalance between proinflammatory and anti-inflammatory cytokines, and genetic origin as risk factors. Such similarities unite the two pathologies and this relationship has been investigated for decades, although the mechanism that unites them is unknown. Studies show that the biochemical intersection between both pathologies comes from *Porphyromona gingivalis*, a bacterium present in the oral flora, which would be responsible for expressing Peptidyl Arginine Deaminase (PAD), which can leads to an increase in local citrullination of the generation of APCA peptide bands. Mangat et al. describe that during physiological citrullination, enzymes of endogenous origin, called Peptidyl Arginine Deiminase (PADs), are responsible for generating citrullinated peptides, and the arginine group is replaced by citrulline.

The second success is represented by the cross-reactivity of APCA generated by periodontal microorganisms (Pg) with antigens present in the joint microenvironment, which further aggravates the inflammation associated with RA, since Porphyromonas gingivalis infection would lead to autoimmunity by the ability of bacteria to express the enzyme Porphyromonas gingivalis-Peptidyl Arginine Deaminase (PPAD) involved in the protein citrullination reaction, as mentioned by Walker, et al. in 1999 and Rosenstein, et al. in 2004. This quantitative increase in peptides citrullinated initiates an immune system response, which involves the production of antibodies directed against peptides of endogenous origin and against those of bacterial origin (ACPA) as stated by Reichert, et al. (2015) and such an amplification of the autoimmune reaction would end in the chronic and damaging inflammation that characterizes arthritis [19].

A study by Laugisch, et al. 2016, clarified that the activity of PAD and PPAD is higher in patients with RA/PD than in the control groups observed in the study ($p=0.038$ and $p=0.004$, respectively), this demonstrates the activation of the enzyme by the bacterial activity of Pg, which in epithelial cells can also perform citrullination in other tissues. Kriauciunas A, et al. in their 2019 study indicated that the persistence of *Porphyromonas gingivalis* bacteria in the oral cavity can affect the etiology of rheumatoid arthritis. Regarding the effect of the PPAD enzyme, the results showed that the bacteria that produce this enzyme disturbs not only the balance of amino acids, but also the immune system of the whole body. Also, the study showed that patients with rheumatoid arthritis improved or were completely cured when periodontal disease was treated. Many clinical and epidemiological studies demonstrate the strong links between RA and PD, in (Table 1) we see the similarities shared between the two pathologies.

Table 1: Similar aspects between rheumatoid arthritis and periodontal disease described in the literature.

	RA	PD
Prevalence	Around 1% of the world's population is affected by RA, being 3 times more frequent in women.	The prevalence of PD is 20% to 50% worldwide.
Risk factor	The strongest associations between women, the shared epitope genetic factor (HLA), and tobacco exposure. Environmental factors such as diet and lifestyle, obesity, red meat, low levels of vitamin D, and microorganisms are also associated.	Periodontopathogenic microorganisms in the oral cavity, exposure to tobacco and alcohol, diabetes, obesity and metabolic syndrome, osteoporosis, low intake of calcium in the diet, stress, and genetic factors are also associated.
Evidence supporting bacterial etiology	There is a change in the microbiome, "dysbiosis", that can cause an autoimmune disease in people with genetic predisposition and environmental factors. Gram-negative anaerobic bacteria responsible for expressing the PAD enzyme have been reported to be strongly associated with RA: P. gingivalis, Prevotella intermedia, and Tannerella forsythia.	There are 13 very abundant and highly prevalent genera in the sampled population: *Streptococcus, Corynebacterium, Capnocytophaga, Haemophilus/Aggregatibacter, Fusobacterium, Prevotella, Leptotrichia, Veillonella, Neisseria, Rothia, Actinomyces, Lautropia*, and *Porphyromonas*. The Prevotella genus has increased in subgingival communities.

Destruction of tissues and bones	Destruction of the cartilage, alteration of the subchondral bone, and formation of osteophytes. There is a proliferative synovitis that causes the destruction of this cartilage and bone.	Destruction of connective tissues of the periodontium and alveolar bone.
Inflammatory markers	PGE2, TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-18, IL-33, granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte colony-stimulating (M-CSF), RANKL, MMP and NO, all found in synovial fluid. There is also E2 (PGE2), IL-6, and IL-1β, which promote bone resorption through osteoclast activation.	In the periodontal condition, there is Prostaglandin E2, Matrix Metallo Proteinase (MMP), and Nitric Oxide (NO). In addition, there is an increase in TNF-α, IL-1β, IL-6, IL-11, and IL-17-inducing osteoclastogenesis. IL-17 and RANKL were shown to be upregulated and IL-10, an anti-inflammatory cytokine, and TGF-β1 to be downregulated in active periodontal lesions.
Autoantibodies	ACPA and FR are produced on a genetic basis such as HLA-DR, and environmental factors such as periodontal disease and smoking. ACPAs are deposited at the citrulline site on CD68-positive RA synovial cells, and bone and cartilage damage are observed in RA.	PD patients demonstrated a high frequency of ACPA. Citrullinated protein and ACPA were found to be contained in the saliva. In particular, Porphyromonas gingivalis infection can increase the amount of ACPA in saliva, indicating a relationship between periodontitis and RA.

Bender P, et al. 2017, conducted a systematic review demonstrating that patients with RA had an immune response against P. gingivalis, which is directly related to the rheumatoid arthritis disease process due to citrullination and by the induction of anti-citrullinated peptide antibodies, which demonstrates that there is a reaction of the immune system to human citrullinated self-proteins. With the evolution of periodontal disease and the production of enzymes by microorganisms, the extracellular matrix is released, exposing intracellular materials of type 1 collagen and fibrinogen, factors that can act as autoantigens when inserted into the environment. It should be noted that the enzymatic modification of antigens, such as the citrullination process, develops autoantibodies. Furthermore, the production of Matrix Metallo Proteinases (MMPs) by pathogenic bacteria directly damages tissues and induces an exacerbated production of MMPs by immune cells, leading to further tissue degeneration; this increase in cytokines and chemokines stimulates a large release of other proteolytic enzymes by leukocytes that end up acting together with the MMPs [20].

The error that occurs in the processes of self-tolerance related to the start of the production of autoantibodies in genetically susceptible individuals may be the cause of the production of antibodies to citrullinated proteins in the synovium and thus the development of Rheumatoid Arthritis. Concomitantly with these biochemical factors that link periodontal disease and rheumatoid arthritis, P. gingivalis is the only bacterium capable of producing the PAD enzyme, which favors the link between these two pathologies. Sato, K. and his collaborators in 2017, reported in their research that P. gingivalis can survive in extreme places, such as the pH of 1.5 to 2 of gastric juice, and scientific evidence shows that this bacterium may be related to negative impacts on the intestinal microbiota, such as dysbiosis. Another experimental study in mice showed that the progressive and constant inoculation of this bacterium in the intestine can cause intestinal dysbiosis, which can exacerbate the processes of inflammatory disorders related to rheumatoid arthritis.

New Associations Between Periodontal Disease and Rheumatoid Arthritis

Pathogenic Microbiota

The human intestinal tract is populated by trillions of microorganisms that cohabit with the host and are responsible for essential functions such as metabolizing vitamins and producing nutrients. The metabolic potential of the intestinal microbiota is also observed in the maintenance of cellular homeostasis by carrying out activity and stability in the metabolism of drugs and other xenobiotic components, for example, drugs used to treat RA that depends on anaerobic bacteria present in the colon to be effective. Studies reveal that an important factor for the development of RA is the intestinal microbiota, as demonstrated by the study carried out in mice raised free of germs (GF) or treated with antibiotics that did not develop RA. However, by inoculating specific microbes from the intestinal tract, GF animals ended up developing RA, concluding that the intestinal microbiota is fundamental in the development of the disease [21].

In a large study by Zhang, et al. to investigate the gut microbiome in RA patients, metagenomic sequencing was performed on 212 fecal samples (77 RA untreated subjects and 80 unrelated healthy controls; 17 RA untreated subjects). RA matched with 17 healthy subjects; and 21 samples from DMARD-treated subjects with RA. The study demonstrated that there were compositional and functional changes in the gut and oral microbiomes associated with RA. The subject of microbiological analysis has been studied by scientists in its various facets, as is the case of the study conducted by Lopez-Olivia I, et al. in which 22 patients with RA and 19 without RA control were examined. Some species were more abundant in RA patients, including the genera Actinomyces, *Cryptobacterium, Dialister, Desulfovibrio, Fretibacterium, Leptotrichia, Prevotella, Selenomonas, Treponema*, and *Veillonellaceae* [G1]. In contrast, some species belonging to the genera *Aggregatibacter, Gemella, Granulicatella, Haemophilus, Neisseria* and *Streptococcus* were not only less abundant, but also less frequent in RA patients.

The results demonstrated that even in periodontally healthy RA patients, gram-negative anaerobic microorganisms are significantly more abundant in RA, which is consistent with a dysbiotic state, emphasizing a link between the oral microbiome and RA. Scher JU, et al., suggests that it is possible that other strains of *Porphyromonas*, in combination with overabundant bacteria from other genera such as *Anaeroglobus* or *Prevotella* (and/or less abundant such as Actinomycetales) may also play a role as potential pathogenic triggers, particularly in the gut microbiota. for being abundant, highlighting its role in RA. In their 2017 study, Schmickler J. et al. revealed that P. gingivalis and F. nucleatum were found at higher concentrations in RA and aCCP-positive patients, and P. intermedia at higher concentrations in RA RF-positive patients. Mikuls TR, et al. found in their study that the association of PD with established RA did not depend on evidence of

prior infection or colonization of subgingival Pg and found no difference in antibody concentrations or the presence of subgingival Pg in RA cases compared to controls in his study. In contrast, elevated levels of circulating antibodies against F. *nucleatum* were detected in RA cases. Wang X, et al. had similar findings and detected F. *nucleatum*, *Bergeyella* sp. in paired samples of amniotic fluid and umbilical cord blood, suggesting the ability of these microorganisms to invade the fetal compartment. These findings corroborate the hypothesis of our review that the circulating oral microbiome exerts a great influence on the pathogenesis of RA and this goes beyond Pg infection [22].

Intestine, Porphyromona Gingivalis and RA

Brandtzaeg P. in 2001 already described that Inflammatory Bowel Disease (IBD) includes two other chronic clinical pathologies that destroy tissues Crohn's Disease (CD) and Ulcerative Colitis (UC)- both apparently caused by an exaggerated immune reaction (hypersensitivity) to commensal disease-causing intestinal bacteria, and similar to what is seen during acute mucosal infections, both CD and UC are characterized by the growth of proteobacteria phyla, particularly the family *Enterobacteriaceae* and *Fusobacteriaceae*, as described by Frank DN, et al. In addition to changes in the GIT, Carding S, et al. in their research, demonstrated that an intestinal microbial dysbiosis is also observed in extraintestinal diseases and, in particular, those that can affect the 'gut-brain axis' affecting the CNS, behavior and cognitive function and by compromising the Hypothalamic-Pituitary-Adrenal (HPA) axis. Commensal bacteria are capable of making brain changes through GABA, this is a key receptor in the CNS since it regulates psychological and physiological processes, so the influence of these microorganisms can stimulate neuronal changes within the CNS, as described Mawdsley JE, in 2005 in their review study and Li H, in 2010. In a recent study published by Yu-Chen Lee, et al. 11 amplicon sequence files from fecal samples from CD patients and eight amplicon sequence files from control fecal samples from volunteers were analyzed. A large increase in the number of Porphyromonadaceae was observed in samples from CD patients compared to control patients. This suggests that *Porphyromonas gingivalis* (Pg) may influence the clinical signs of CD, corroborating the study by Tsuzuno T. et al., in which Pg altered intestinal barrier function in rats [23,24].

Porphyromonas gingivalis has a high cholinogenic potential as it has virulence factors including gigipains (RgpA, RgpB and Kgp), which are considered the key Pg virulence factors as they are proteases capable of degrading numerous host proteins, mainly cytokines and host cells. surface proteins. A systematic review by Fiorillo L, et al. to assess a correlation between the periodontal implications of P. gingivalis and other proven correlated systemic diseases, showed that a state of constant inflammation caused by Pg, or even bacterial bloodstream or bacterial products, may be responsible for other systemic conditions, such as rheumatoid arthritis, diabetes, neurology, immunology, oncology, and bacteremia with systemic diseases.

The studies that support the concept that the appearance of autoimmunity is linked to the gastrointestinal tract are the following:

a) The microbial plankton in individuals with early RA differs from controls, with a reduction of microorganisms inherent to the family *Bacterioides* and *Bifidobacterium*, and an increase in bacteria belonging to the genus Prevotella.

b) In murine models, after parenteral injection of cell wall particles from various intestinal microorganisms, an arthritogenic action was found to occur and in this model, arthritis does not develop when reared under conditions favorable to germs. FG); on the contrary, it appears when intestinal bacterial species have been introduced [25].

c) The host diet has been shown to directly stimulate inflammatory levels.

d) Regarding therapy, certain medications used to treat RA have antimicrobial effects (chloroquine, sulfasalazine, minocycline, and roxithromycin).

e) Regarding the microbiome, when altered, it was partially restored to normal in patients who showed clinical improvement after prescribing disease-modifying antirheumatic drugs. Thus, differences in the composition of the intestinal microbiota and in the function of the immune system can define which individuals will develop the disease.

Numerous lymphocytes are present in the Gastrointestinal (GI) tract as part of this host-commensal relationship, such as IL-17-expressing T cells (Th17), as well as regulatory T cells (Treg), which have an activated phenotype and have a crucial importance for a successful relationship between the host and the microbiota. Specific groups of commensal microorganisms play different roles in this relationship: such as Segmented Filamentous Bacteria (SFB) and members of Clostridium groups IV and XIV that promote the induction of Th17 or Treg cells, respectively [26]. Later, other findings demonstrated the relevance of intestinal commensal microorganisms in different types of immune cells, both in innate and adaptive immunity. Studies carried out in K/BxN mice demonstrated how the development of joint inflammation occurs through FBS, that is, K/BxN arthritis strongly depends on IL-17, and the appearance of IL-17-producing Th cells both in the gut as in the gut in the spleen it is critically dependent on gut microbes, in particular FBS.

During the evolution of research aimed at discovering the mechanisms linking RA to PD, it was shown that there is a large and complex relationship between an individual's gut microbiota and their own immune system in maintaining homeostasis. Processes such as diseases, changes in dietary patterns, from the increase in the number of specific bacteria in the microbiota to new colonizations can be responsible for the deregulation of homeostasis, that is, a dysbiosis that can favor the development of autoimmune diseases. Research carried out in mice with Collagen-Induced Arthritis (CIA) showed that the administration of antibiotics caused an increase in the proinflammatory cytokines IL-6, TNF-c and IL-17, culminating in the worsening of the disease (RA). When the intestinal microbiota of mice susceptible to collagen-induced arthritis was compared with that of resistant mice, the following results were obtained: Prevotella, Desulfovibrio, Odoribacter, Parabacteroides, Acetatifactor, genera Ruminococcus, Coprococcus, Blautiai, demonstrating that the intestinal microbiota caused a difference between animals with CIA-induced disease and those resistant to CIA.

Oral Pathogens and Rheumatoid Arthritis

Establishing a connection between adverse systemic conditions and oral infections has required a great deal of effort on the part of the scientific community. Evidence demonstrates that systemic spread of oral commensals and pathogens to distant sites in the body can cause extraoral infection and inflammation. Experiments with murine placentas suggest that oral commensal species may translocate and become pathogenic elsewhere. In a case-control study examining longitudinal relationships between dental bacterial load and maternal antibody response in relation to pregnancy outcome, dental bacteria tended to be increased in mothers who delivered preterm, while levels remained relatively low. stable in mothers delivering at term. To test the mobility of the oral microbiota, Témoin S, et al. conducted a study that demonstrated the presence of periodontal pathogenic bacterial DNA in the synovial fluid of patients with arthritis who had prosthetic joints and RA. In the presence of periodontal disease, the number of oral bacteria increases dramatically, increasing the chances of these bacteria entering the bloodstream [27].

Since 1998, studies have concluded that *Porphyromona gingivalis*, a

gram-negative, periodontal pathogenic bacterium, is directly associated with exacerbation of the rheumatoid arthritis disease process and this microorganism is largely responsible for causing changes in the behavior of the intestinal microbiota with the ability to cause dysbiosis by increasing the permeability of the intestinal mucosa, resulting in the highest percentage of citrullinated proteins due to the action of releasing peptidyl arginine deaminase that acts on arginine peptides. Although P. gingivalis is considered a trigger for the appearance of RA due to its high capacity to citrullinate peptides through a specific enzyme, Porphyromona Peptydyl Arginine Deiminase (PPAD), and thus generate new antigens and Anti-Citrullinated Protein Antibodies (APCA) in post-translational modification, previous studies showed that P. gingivalis was not present in the subgingival biofilms of RA patients.

A species from the phylum Bacteroidetes, P. copri, has also been associated with RA. When fecal samples from RA patients containing dysregulated amounts of P. copri were administered to SGK mice (=zeta-chain-associated protein kinase (TCR); mutation 1, Shimon Sakaguchi mice), Th17 levels increased along with severity of disease. arthritis (Maeda, Y. et al., 2016). Another 2018 study by Lucas S, et al, showed that the *Prevotella* genus can influence bone loss by controlling the levels of Short-Chain Fatty Acids (SCFAs) that mediate host osteoclastogenesis. Marietta EV, et al. demonstrated that the member of the *Prevotella genus*, Prevotella histicola, inhibited the evolution of ASD in humanized mice carrying the HLA-DQ8 alleles. This effect was mediated primarily through modulation of Th17/Treg balance via CD103+Dendritic Cells (DCs) and myeloid suppressors, but without affecting innate pathways involving Toll-Like Receptors (TLRs). These studies reveal that the oral microbiome and its interaction with host mucosal immunity probably play a key role in the development of RA, especially when there is a dysbiosis of this environment [28]. Recently, in a German study, dysbiosis was identified in subjects serologically positive for ACPA or RF (preclinical AR) with 16s sequencing compared to controls, and the genus Prevotellaceae was present at >1% abundance in 53% of subjects with preclinical RA. Individuals with abundant Prevotellaceae had a higher prevalence of RF positivity, but no other clinical features [29].

Bacteria such as P. intermedia and Tannerella forsythia were found in the oral flora, as well as high levels of antibodies against these microorganisms in the serum and synovial fluid of patients with RA, which suggests the presence of these bacteria in the synovial fluid of these individuals. Another periodontal pathogen that may also contribute to protein citrullination by pathways other than P. gingivalis is A. actinomycetemcomitans (Aa) through the production of leukotoxin-A (LtxA), as described by Konig MF, et al. in their study, and Aa-mediated damage during periodontal infection may be sufficient to generate the antigenic markers recognized by disease-specific autoantibodies in RA. Scientists have associated periodontal disease and its various bacterial species with the great potential to activate the individual's endogenous PAD, however, it is necessary to study which periodontal pathogens are capable of hypercitrullinating the host cell. What was observed is that LtxA, in addition to being the main virulence factor of Aa in the host, induces plasma membrane permeabilization and unregulated calcium entry into the toxin-sensitive. Mukherjee A, et al., suggest that leukocyte strains of Aa may cause an arthritogenic autoimmune challenge found in humans. In addition, it is consistent with the innovative idea that it is unlikely that the existence of a single pathogen can act, by itself, as a motor in the development of autoimmunity in all cases of RA, since this relationship between microorganisms and arthritis is more complex. than what Koch's postulates preach [30].

Treatments Used

Current Treatments for Periodontal Disease

Periodontal disease, as mentioned, refers to the chronic process of the acute inflammatory process generated by gingivitis. Thus, it is necessary to use health promotion to avoid as far as possible the appearance of acute inflammation with the potential for chronicity. For this, initially, it is necessary to raise awareness about the importance of proper oral hygiene Oral hygiene processes aim to reduce the microbial quantities present in the oral cavity, as is the case of dental biofilm, as proposed by Loe H, et al. 1965, and for this, several studies were developed looking for the need for an interval for biofilm reduction with a variation of 24 to 48 hours. T.M. and his colleagues in 2013 concluded that removal of dental biofilm within 24 hours was essential to reduce rates of gingivitis within 30 days.

In addition, some people may have dental calculus that favors the attachment of dental biofilm and can also serve as a chronic irritant to periodontal tissue. As a consequence, clinical treatment of desquamation is necessary to eliminate these irritating and risk factors for the development of periodontal disease, since the calculus can also become a refuge for the formation of bacterial plaque. The chronification of this structure, added to the bacterial biofilm responsible for periodontal pathology, can cause everything from gingivitis to chronification, as is the case with periodontal disease. In this way, there is a need to carry out a desquamation treatment for the adequacy of oral hygiene, as is the case with manual desquamation and that promoted by ultrasonic devices [31].

Along with mechanical treatment measures, the literature indicates cases of administration of antimicrobials in order to reduce the bacterial load of the red complex that causes periodontal disease processes. Among the drugs are: chlorhexidine, tetracycline and metronidazole. Jepsen K. and Jepsen S. in their large study published in 2016, show that this treatment route can bring benefits to patients in certain cases, so it is necessary to assess the needs of each patient. Considering the weight between potential side effects and decreased bacterial rates, collaborating to reduce the frequency of new periodontal pockets and the depth of existing ones, as reported by the systematic review. In addition to avoiding the uncontrolled use of these drugs so as not to collaborate with the formation of resistant bacteria [32].

Current Treatments for Rheumatoid Arthritis

As already mentioned, rheumatoid arthritis is a disease that begins long before its signs and symptoms. And because of this, the earlier the disease is discovered, the better the patient's response to treatment, such as reduced joint damage. Currently, there are several drugs available for the treatment of the pathology, such as glucocorticoids, nonsteroidal anti-inflammatory drugs, synthetic disease-modifying antirheumatic drugs (methotrexate) and biological drugs (responsible for modifying costimulation, interleukin inhibitors). 6 and tumor necrotizing factors). As in any disease-health process, there are particularities of each individual in terms of treatment, but the European League Against Rheumatism recommends administering methotrexate as soon as rheumatoid arthritis is diagnosed and, if there is rejection by the body, leflunomide or sulfasalazine. serve as methods of alternative therapies. Concomitant to this administration, there is a recommendation on the use of intra-articular injections [33,34].

Considering the amount of discussion in the scientific literature related to the use of drugs for treatment, it appears that the administration of methotrexate with tumor necrosis factor inhibitors during the initiation of treatment followed only by maintenance of the disease-modifying antirheumatic drug synthetic origin (methotrexate), suggests a reasonable pathway for remission and reduction of rheumatoid arthritis-related damage, as suggested by the meta-analysis by Emamikia S, et al. 2016. Additionally, one study demonstrated that therapy with tocilizumab, an interleukin 6 inhibitor, in combination with methotrexate resulted in less radiographic damage after 3 years. In oral conditions, there are drugs such as Tofacitinib and Baricitinib, both inhibitors of the janus kinase enzyme. In the literature, there were controversies regarding administration. The study by Scott C. I. and

colleagues in 2018 concluded that there is a lack of conclusive data to be able to relate the use of these inhibitors with thromboembolic factors, highlighting that rheumatoid arthritis can culminate in an increase in thrombotic factors. Author Scott and his team consider evaluating the patient for pre existing factors related to thrombosis before prescribing these Janus kinase inhibitors. Despite this discussion, some studies have shown the safety and positive results after the administration of these drugs. Finally, there are several strategies documented in the literature, some proven and others in conflict by scientists, but in reality, the best alternative is early diagnosis of rheumatoid arthritis and medical follow-up to seek remission of the pathological process with certain conditions. strategies in order to generate fewer harmful processes for the individual.

Treatment of Rheumatoid Arthritis and Its Relationship with Periodontal Disease

The correlation between diseases is becoming clearer and more objective, not ruling out the need for more studies looking for similarities and interferences between RA and PD. To better understand, it is worth mentioning that the individual's inflammatory response, their genetic susceptibility and the microbial principles found are basic principles for this correlation to exist. However, there is evidence that certain therapies for rheumatoid arthritis can lead to a decrease in inflammatory rates in periodontal tissues, as is the case with TNF blockers. However, other research shows that the pharmacological relationship of NSAIDs can bring both periodontal improvement and unwanted complications [35].

Effect of Modulating Therapies on Periodontal Disease

Given the probable bidirectional relationship between both diseases and the chronic inflammatory process, a key pathological element in both, it is reasonable to assume that the treatment of rheumatoid arthritis, based on host-modulating therapies, could have a significant impact on the periodontal status of rheumatoid arthritis. patients with periodontitis Considering the chronic inflammatory process together with the probable mutual relationship between both pathologies, the studies show that the treatment of rheumatoid arthritis with modulating therapies can directly influence the periodontal condition of the arthritis in these patients. In a study by Perls, et al. they suggested that blockade of TNF-α alpha activity directly influences patients with periodontal disease. This cytokine is widely used to treat chronic inflammatory bone diseases such as rheumatoid arthritis. Another study, carried out by Ortiz et al, showed that periodontal treatment associated with anti-TNF therapy produces a greater improvement in periodontal status than monotherapy.

Another study by Kobayashi et al showed that the specific inhibition of the IL-6 receptor for the treatment of patients with rheumatoid arthritis showed a significant improvement in clinical periodontal condition. As well as the recent study by Ancuța et al that explored the role of IL-6 receptor blockade in patients with rheumatoid arthritis and periodontitis, which corroborates Kobayashi's idea, where arthritic and periodontal parameters were improved. These studies suggest the advantage of combined periodontal and cytokine-targeted therapy on clinical outcome [36]. Therefore, it is feasible to consider the use of cytokine-targeted therapies as an adjuvant approach for the prevention or treatment of periodontal diseases in RA patients with elevated circulating levels of inflammatory cytokines, such as TNF and IL-6.

Effects of Periodontal Treatment in Rheumatoid Arthritis

Due to the successive studies that support a true association between periodontitis and rheumatoid arthritis, we can admit the importance of periodontal treatment to improve the inflammatory markers of rheumatoid arthritis, as well as its clinical and biochemical expression. Regarding the biomarkers of RA after periodontal treatment, studies suggest that the Erythrocyte Sedimentation Rate (ESR) decreases significantly in RA patients after non-surgical periodontal treatment. In relation to C-Reactive Protein (CRP), a systemic inflammation marker widely used to determine the appearance of RA, it was reported that this biomarker is not influenced by non-surgical periodontal treatment, according to Okada M, et al. 2013. Thus, to determine the serum levels of Rheumatoid Factor (RF), Okada, M. et al demonstrated that there is no statistically significant difference after non-surgical periodontal treatment in patients with RA and PD. However, for the evaluation of Anti-Citrullinated Protein Antibodies (ACPA), a specific molecule for the presence of RA, studies have shown that non-surgical periodontal treatment can decrease this protein in patients with periodontitis and RA. Lappin DF, et al. 2013 performed non-surgical periodontal therapy in patients who had periodontitis with rheumatoid arthritis and demonstrated a significant decrease in the levels of anticyclic citrullinated peptide and anti-P antibodies non-surgical periodontal therapy [37,38].

New Perspectives for Treatments

The assertive use of probiotics brings benefits for the treatment of periodontal disease, as shown by the use of B. latics HN019 to complement the scaling and root planing procedure or for non-surgical treatment. This is due to its antimicrobial properties and help to the immune system, other research points to the application of L. reuteri in order to reduce the microbial contingent that causes periodontal disease and has the ability to reduce peri-implant mucositis as well as being beneficial in helping to prevent it From this, it is suggested that the intake of probiotics by the individual does not necessarily have to be associated with a therapeutic purpose, but as a quality-of-life condition, as shown by the research by Slawik S, et al. Probiotic microorganisms brought clinical improvements in the oral condition of patients affected by gingivitis [39].

As has been reported, dysbiosis can be a triggering factor for the appearance of autoimmune antigens for the generation of Rheumatoid Arthritis, so probiotics can be a determining factor to help prevent and improve the conditions of the intestinal microbiota, as evidenced by the research by Vaghef-Mehrabany E, et al. in 2014 on the use of L. casei 01 associated with the improvement of inflammatory signs and rheumatoid arthritis, also made it clear the need for further research in this area to develop adjuvant therapy. Research indicates that the use of probiotics can reduce inflammatory cytokines (IL-6, TNF and IL-1), enzymes such as cyclooxygenase-2 (COX-2) and even the edema caused by the disease. However, the use of probiotics still needs further study in the current scientific literature to prove its positive or irrelevant effects, as some studies have shown, as Haber, A. L. and colleagues also showed in 2017 in their research with 60 sick patients, in those who 30 received probiotics and 30 placebo for 12 weeks, noted that there was no significant improvement in oxidative stress, so they did not have therapeutic potential for the disease. Having the research present in the scientific literature, the need to produce new research for the production of literary and clinical knowledge on the use of probiotics as adjuvants to help in the quality of life of patients is evident [40].

One of the protocols considered innovative and under study in both medicine and dentistry is the use of Photo Dynamic Therapy (PDT). Through a diode laser with a specific wavelength and a photosensitizer, it is possible to penetrate deep periodontal pockets, reducing local inflammation. However, to date there are no studies that have evaluated PDT treatment in periodontal and RA patients. In a randomized clinical trial by Harmouche, et al. PDT was shown to significantly improve the reduction of residual pockets >5mm over a 6-month period and was beneficial for deep, swollen/bleeding pockets at sites with depth of penetration Probing. A study conducted in patients with mild RA and periodontitis showed that PDT significantly improved clinical and biochemical periodontal outcomes in patients with RA; however, future clinical trials are needed [41].

A new alternative for the treatment of rheumatoid arthritis would also be PFT associated with Cu 7.2 S 4 combined with NIR (808nm, 1Wcm-2). This combination of ions acts on bone preservation, includ-

ing increased Bone Mineral Density (BMD) and bone volume/total volume, as well as inhibiting inflamed synovial invasion, cartilage erosion, and expression of proinflammatory cytokines in vivo, among other mechanisms of inflammation. disease suppression. Therefore, recent studies show that combined PTT (Photothermal Therapy) and PDT (Photodynamic Therapy) can be a new treatment modality for RA with its full potential. Given the various alternatives to evaluate the association at the drug level and the difficulties in evaluating the impact of the treatment of both diseases in humans, a study in an animal model may be useful to test the different treatment groups before their translation to humans, and this is currently being done in our research group to collaborate with the resolution of future questions [42].

Future Prospects and Conclusion

Currently, new substances are gaining ground in the scientific area, such as Celastrol, which comes from the roots of *Tripterygium wilfordii* and *Tripterygium regelii*. There is evidence that proves its efficacy in anti-inflammatory effects related to rheumatoid arthritis. Its effect is to inhibit an important nuclear transcription factor (NF-kB). However, since it is a new and future perspective, it is necessary to carry out more studies in the area to understand its cytotoxic capacity and its forms of action. Based on this, An Lemei, et al. 2020, associated the substance with nanoparticles in mice with induced rheumatoid arthritis and there was a suppression of the inflammatory response with effective accumulation in the joints affected by rheumatoid arthritis, resulting in the attenuation and improvement of clinical symptoms. Biocompatibility, nanoparticle targeting, correct drug release at the required active site, and low toxicity proved to be effective in the proposed treatment in mice. Based on this, a case arises for future research with nanoparticles and the substance for the evolution of treatments for rheumatoid arthritis. While for periodontal disease, nanoengineering becomes an area of knowledge that has not yet been explored, which allows further research on this association of diseases.

Currently, there is a definitive therapy for periodontal disease that aims to recover the tissues lost due to the disease through works developed from biomaterial engineering, whose treatment has a wide spectrum to be explored by science. The use of biomaterials such as membranes composed of support materials, guide, genes, proteins, antimicrobial agents and even factors that stimulate tissue growth. In addition to its high capacity for aesthetic recovery, this therapy is very interesting in order to return the reabsorbed tissues to the patient and even enable treatment with implants [43].

Still in periodontal disease, there is research and studies related to the regenerative treatment of tissues with oral mesenchymal stem cells, in addition to having immunoregulatory capacity because they self-regulate through inflammatory processes and proinflammatory cytokines, that is, stem cells can be differential in the course of periodontal disease in order to decrease the inflammatory processes that result in the degradation of the supporting periodontal tissues. The use of mesenchymal stem cells also brings benefits for the treatment of rheumatoid arthritis, since it has immunosuppressive potential, therapeutically attenuating the process of tissue degeneration. This feature is due to cell-cell interaction and the presence of proinflammatory cytokines, such as interferon gamma (IFN-γ) [44].

The use of gene therapy is a new avenue in science that has positive potential in the treatment of periodontal disease, as researcher Racz G.Z. and his team demonstrated in their 2014 study on the use of gene therapy improving outcomes. therapeutic use of stem cells. Gene therapy can be made possible by the introduction of viral agents, such as a retrovirus, or even by stem cells, as mentioned above. The use of this route showed promising results in the study in rats carried out by the researcher Tsuchiya, S. and his collaborators in 2017, since it was possible to present a greater tissue recovery compared to the control group. This occurred through the induction of growth factors associated with biomaterials. Finally, based on our investigation, we highlight the importance of carrying out more studies focused on the common pathogenic mechanisms of periodontal disease and rheumatoid arthritis, in addition to their treatment methods. Also, there is a large branch of discoveries triggering new treatment approaches in order to improve the prognosis of both diseases and tissue recovery. For example, mesenchymal stem cell-associated gene therapy has shown promising results controlling exacerbated inflammatory foci with protection against tissue loss.

As demonstrated by the large study developed by Nakao, Y. and colleagues in 2021 in a mouse model, the use of mesenchymal stem cells from gingival tissue that have been preconditioned with proinflammatory cytokines such as tumor necrosis factor alpha (TNF-ÿ) was able to provoke the polarization of macrophages, culminating in a decrease in the aggressiveness of the inflammatory process in the periodontal tissues of the study rats. In addition to the therapeutic potential, the ease and accessibility of these cells is considered. In conclusion, the relationship between periodontitis and rheumatoid arthritis is a fascinating and evolving area of medical research. This review explores possible links between these two conditions, suggesting that chronic gum inflammation can trigger and exacerbate rheumatoid arthritis. Therefore, a multidisciplinary approach and precision medicine will consider them not as isolated conditions, but their interactions and therapeutic targets.

Additionally, new treatments are being developed to address this complex relationship. Therapeutic approaches that aim to control periodontitis and reduce oral inflammation may have significant benefits in the management of rheumatoid arthritis. This highlights the need for closer collaboration between rheumatologists and dentists to improve patients' quality of life. As research continues to advance, we are likely to have a deeper understanding of the links between periodontitis and rheumatoid arthritis, as well as better treatment options. Early diagnosis, prevention and treatment of periodontitis can play a crucial role in reducing the risk and managing rheumatoid arthritis.

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