Chapter

The Complex Relationship of Periodontal Disease and Rheumatoid Arthritis

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Abstract

The relationship between periodontitis and systemic diseases is an important part of clinical periodontal research, which has been growing steadily. Even though the etiologies of periodontal disease and rheumatoid arthritis (RA) differ, these pathologies have many common features, both being multifactorial diseases characterized by localized chronic inflammatory reactions, which are fuelled by an analogous set of cytokines (among many, the most prominent being Tumour Necrosis Factor (TNF), Interleukin (IL) 6 and 17), leading to high systemic circulating concentrations of inflammatory markers such as C-reactive protein (CRP). It was not until the discovery of peptidylarginine deiminase (PAD) mediated citrullination of proteins by *Porphyromonas gingivalis* that the link between the two diseases was purely speculative. This citrullination initiates a series of events which culminate in the production of anti-citrullinated protein antibodies (ACPA) and, finally, in the clinical manifestation of rheumatoid arthritis. Another common denominator is the bone destruction caused by proinflammatory cytokines secreted by T 17 helper cells (TH17) which is the pathological hallmark of both diseases. Other notable common areas are shared risk factors such as environmental and genetic risk factors. Regarding treatment, neither pathologies have a definitive cure, however, several strategies are employed, some of which are common, such as diet and lifestyle changes, and immunomodulating medication applied locally or systemically.

Keywords: periodontal disease, rheumatoid arthritis, cytokines, DMARDS, treatment, microorganisms

1. Introduction

The relationship between periodontitis and systemic disease is an important part of clinical periodontal research, which has been growing steadily since the late 1980s. Monsarrat et al., in 2016 stated that approximately a third of all recent periodontal studies address this issue [1]. Moreover, in the same year Loos published the

results of a study, accrediting the fact that a total of 57 different systemic diseases are being investigated for possible links [2].

This relationship is often described as "bidirectional", but the design of many epidemiological observational studies does not allow the relationship to be firmly established and, implicitly, any identified associations will be bidirectional until clarifying data appear. At present, there is no full understanding of the importance of the multiple associations reported and especially whether they play a causal role.

Although having different etiologies, periodontal disease (PD) and rheumatoid arthritis (RA) have many common features, both being multifactorial diseases characterized by localized chronic inflammatory reactions, which are fed by an analogous set of cytokines (Tumour Necrosis Factor (TNF)-α, Interleukins (IL) 6 and 17), leading to high concentrations of inflammatory markers such as circulating C-reactive protein (CRP) [3]. In addition, bone destruction caused by proinflammatory cytokines secreted by helper T cells (TH17) is the pathological hallmark of both diseases. Furthermore, periodontitis and RA have certain risk factors in common such as environmental and genetic [4].

Rheumatoid arthritis is a chronic, autoimmune systemic inflammatory disease, characterized by an arthropathy with chronic, progressive, deforming and destructive evolution, having a major disabling character and multiple systemic manifestations that determine an important premature mortality. It affects 0.5-1.0% of the world's population, the cause however is still unclear [5]; having said all this, it is thought to be triggered by a combination of genetic and environmental factors that lead to the degradation of immune tolerance at the interface with mucosal surfaces, specifically in the lungs, intestines, and periodontium [6]. The effect is the triggering of the autoimmune response characterized by the production of rheumatoid factor (FR) and ACPA (anticitrullinated protein antibodies). Binding of ACPA to citrullinated epitopes in joints and the formation of immune complexes containing rheumatoid factor helps to form a vicious circle of tissue damage involving the activation of synovial macrophages and dendritic cells, and the release of proinflammatory cytokines and enzymes that lead to tissue degradation. At the same time, peptidilarginine deiminases (PAD) released by neutrophils during necrosis or during the production of extracellular traps citrullinate the proteins in the joints, resulting in a continuous local immune response that is self-sustaining [7].

Until a few years ago, despite these common features, it was difficult, if not impossible, to establish a potential causal link between the two diseases. The discovery and characterization of an enzyme uniquely expressed by the major pathogen in periodontal disease *Porphyromonas gingivalis*, namely peptidilarginine deiminase (called PPAD to distinguish this bacterial enzyme from human peptidilarginine deiminase - PAD), was the basis for the hypothesis that protein citrullination mediated by PPAD originating from inflamed periodontal sites may initiate a series of events that culminate in the production of anti-citrulline protein antibodies (ACPA) and ultimately in the clinical manifestation of RA [8].

The diagnosis of RA has been revolutionized by the discovery of ACPA, disease-specific antibodies that are present in approximately 70% of patients with this pathology. These are strictly correlated with the severity of the disease and with major risk factors, genetic and environmental, suggesting a pathogenic involvement. They are also detectable in the bloodstream 10 years before the onset of clinical symptoms, suggesting that the initial loss of immune tolerance to citrullinate proteins is most likely a consequence of an inflammatory event that occurs outside the joint [9].

However, most proteins in the human body undergo certain post-translational changes, starting with proteolytic modifications, glycosylation processes or lipid changes, to modifications of residues by chemical or enzymatic means.

These changes represent, in fact, fundamental physiological processes necessary in order for the organism to function normally; however, by the generation of neo-epitopes, these changes can determine the formation of anti-modified protein antibodies (AMPA), for example ACPA, in subjects that are genetically susceptible and are subjected to certain risk factors [10].

As a chronic inflammatory disease, some of the characteristics and pathogenic processes of RA mirror those of periodontitis, both of which eventually result in the progressive destruction of bone. The profound interdependence between these two diseases is the result of common genetic and environmental risk factors, including HLA-DRB1 gene expression, smoking, and other exogenous risk factors such as nutrition, socioeconomic status, and psychological factors (stress). Despite the obvious differences in etiology, there is evidence linking the two diseases, clinically, epidemiologically, serologically and experimentally [11].

2. Immunomodulatory medication in rheumatoid arthritis and its effect on periodontal disease

Given the similarities between the pathogenic aspects of periodontitis and rheumatoid arthritis, it is pertinent that the therapeutic options available for rheumatoid arthritis be known in the periodontal research community but also by periodontal specialists that have rheumatoid arthritis patients in treatment. Although the early mechanisms that result in impaired immune tolerance and the progression of clinical signs and symptoms of rheumatoid arthritis are unknown, the inflammatory cascade plays a key role in all stages of rheumatoid arthritis pathogenesis, from autoimmunity to joint localization and joint destruction [12].

There are several treatment options available for patients with RA, imposed by international treatment guides that are independent of the oral and periodontal status, and these can include physical therapy, lifestyle changes such as diet and exercise in an effort to diminish joint stress, medication and even surgery. Among drugs the most common prescribed are non-steroidal anti-inflammatory drugs (NSAIDs) and so called anti-rheumatic disease-modifying drugs (DMARDs) [13].

The term DMARDs is used to name a group of drugs that are generally unrelated, but differ from NSAIDs (that have the purpose of reducing inflammation but not of treating RA) and also differ from steroids, that reduce the immune and inflammatory response but do not slow the progression of the disease. In other words, while NSAIDs and steroids are used to control RA symptoms, only DMARDS influences the progression of the disease [14].

DMARDS act as immunosuppressive and immunomodulatory agents and are divided in two major groups: conventional and biologic. Regarding the mechanism of action, each DMARD is unique and it is by consequence of the specific pathways it affects in the inflammatory cascade. In clinical practice the most frequently used conventional DMARDS are methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine [13].

Biologics are the other major class of DMARDS made accessible for the first time in the early 90's and are frequently prescribed when conventional therapy is not effective, objectified by clinical or radiological disease progression and on-going disease activity. This type of medication is highly specific and it targets a particular immune system pathway. Biological DMARDs include a number of anti-cytokine agents that block the activity of specific cytokines and are usually monoclonal antibodies that bind to the target cytokine [14]. Examples of biologics include TNF inhibitors (adalimumab, infliximab, certolizumab, etanercept), anti-CD20 (rituximab), anti-CD80 and anti CD-86 (abatacept), anti-IL-6 (tocilizumab, sirukumab),

anti-IL-17 (secukinumab, ixekizumab) and Janus Kinase (JAK) inhibitors (tofacitinib, baricitinib) to name a few [13].

DMARDs determine the reduction of the level of inflammatory markers such as CRP and rheumatoid factor (RF), the rate of erythrocyte sedimentation (ESR), and also cartilage and bone damage. In the treatment of rheumatoid arthritis, therapy with biological DMARDs is often prescribed in combination with a conventional agent in those patients that presented a limited response to conventional anti-rheumatic disease-modifying therapy.

Tumor necrosis factor-alpha (TNF-α) is a particularly important proinflammatory mediator and therefore, one of the primary objectives of the development of anti-cytokine therapies that have been introduced in the treatment of rheumatoid arthritis has been the development of anti-TNFα agents. Other cytokines that play a role in the pathogenesis of rheumatoid arthritis include interleukin-1 (IL-1), interleukin-6, interleukin-17, interleukin-15 and more recently interleukin-23 [14].

Additional studies are needed to better understand these mechanisms and help maintain general health, oral health parameters requiring close monitoring in RA patients.

Periodontal disease therapy by modulating the host response is a high interest subject in periodontology and several classes of drugs have been proposed to fulfil this desiderate, some of them are even used in the treatment of rheumatoid arthritis. Amongst the potential host modulator drugs we mention NSAIDs, corticosteroids, conventional synthetic disease modifiers (DMARDs), matrix-metalloproteinase (MMP) inhibitors, clinically modified tetracyclines, anti-cytokines and biologic therapies, lipid mediators of resolution of inflammation, small molecule compounds, histone diacetylase inhibitors, RANKL inhibitors, bisphosphonates, Toll-like receptor inhibitors and also the combined anti-inflammatory and antibacterial approach [13].

Considering the common proinflammatory pathways between the two diseases, interactions with the immune system and the additional systemic inflammatory burden that accompanies periodontal disease we wanted to assess to what degree specific rheumatoid arthritis drug therapy influences periodontal status and if there is any difference regarding treatment combinations on oral status amongst RA subjects. Furthermore, we wanted to verify whether there is any difference in the severity of rheumatic disease and disease activity according to oral health status.

To accomplish this task we conducted a study on 220 patients with a verified diagnosis of rheumatoid arthritis in which we analysed the local inflammatory status, by evaluating the Quigley Hein (QH) indices, the Lőe and Silness gingival index (GI), the papillary bleeding index (PBI), Probing Depth (PD) and the Community Periodontal Index of Treatment Needs (CPITN), accompanied by a detailed assessment of the systemic status in patients with rheumatoid arthritis, including indexes of rheumatic disease activity but also systemic non-specific inflammatory markers such as C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [15].

There is no consensus in the literature regarding the severity of periodontal disease in rheumatoid arthritis patients, however authors agree that the percentage of moderate to severe periodontitis is higher in RA patients when compared to systemically healthy controls with periodontitis.

In our study, following the periodontal examination, 149 of the total 220 patients with rheumatic pathology were diagnosed with moderate and severe periodontitis, so from a percentage point of view we can say that 67.72% of the analysed group have moderate to severe periodontal damage. These results are similar with those from Erikson [16] who found a percentage of 75% out of 45 patients had moderate or severe periodontitis, Rodríguez-Lozano [17] on the other hand, reported 45% of 187 RA subjects had severe periodontitis and finally another study reported

an astounding 98% (out of 168 subjects) were suffering from moderate to severe periodontal disease [18].

Other than the oral status, from a systemic, rheumatic point of view we analysed the following disease markers:

2.1 Clinical status of rheumatic disease (Stage I to IV)

Stage 1: It is the incipient stage and involves the initial joint capsule inflammation and synovial tissue swelling; causes evident symptoms of joint oedema, stiffness and pain.

Stage 2: Cartilage deterioration due to synovium inflammation which causes more important limitation of mobility.

Stage 3: Due to the substantial inflammation of the synovial tissue the bone is affected, not only the cartilaginous tissue. Subjectively, pain increases marked oedema, loss of muscle vigour and mobility, furthermore, deformations of the joint may appear.

Stage 4: In the ultimate stage of rheumatic disease the joints are no longer functional and the inflammation stops. Subjects experience loss of mobility, stifness, oedema and pain.

On the studied cases, among the patients with rheumatoid arthritis, the distribution of the subjects on the four stages was: stage I - 0.9%, stage II - 11.8%, stage III - 50.9% and stage IV - 36.4%.

2.2 VAS score (Visual Analogue Scale) for pain assessment

VAS (analogue visual scale) is a measuring instrument, often used in epidemiological and clinical research to measure the intensity or frequency of various symptoms. Using a ruler, the score is determined by measuring the distance (mm) on the 10 cm line between the "pain-free" point and extreme pain, providing a range of scores between 0-100.

The VAS pain assessment score ranged from 10-90, with a mean value of 36.55 ± 21.17, which included the study group with a moderate perception of pain.

2.3 DAS28

The DAS28 score (disease activity score) is a measure of disease activity in rheumatoid arthritis, 28 representing the examined joints. The range of measures of disease activity in RA is wide and it includes: assesement of joints for oedema and tumefaction, overall pain scores and general condition, inflammation serum biomarkers (eg ESR - erythrocyte sedimentation rate and CRP - C reactive protein), questionnaires, radiographic examinations, nuclear magnetic resonance and ultrasound.

DAS28 is a composite score, the results are entered into a complex mathematical formula to produce the overall score of disease activity. A DAS28 greater than 5.1 involves active disease, less than 3.2 decreased disease activity, and less than 2.6 remission.

2.4 Rheumatoid factor (RF)

For 86.4% of patients, rheumatoid factor was found to be positive. The correlation of rheumatoid factor positivity with the staging of rheumatoid arthritis showed that 52.6% of patients with positive rheumatoid factor were in stage III of the disease, and 36.8% in stage IV ($p = 0.014$).

2.5 AntiCCP antibodies (ACPA)

63.6% of patients had antiCCP antibodies. The correlation of the presence of antiCCP Ac with the staging of rheumatoid arthritis showed that 51.4% of patients with positive antiCCP Ac were in stage III of the disease, and 34.3% in stage IV ($p = 0.451$).

Among the associated comorbidities, on the studied cases, most frequently, the presence of hypertension (54.5%) and osteoporosis (31.8%) was noticed.

Regarding medication for RA, we observed that the most frequently prescribed were mainly the following: Leflunomide (46.4%) and Rituximab (44.5%), and Methotrexate 23.6%, of all cases, followed by 18.2% Adalimumab and 15.5% Tocilizumab. However, it is important to specify that the majority of patients have a combined medication of 2 drugs. The most frequent combination for our group are the following synthetic DMARDS combined with biological DMARDS: Methotrexate + Rituximab (11.8%) and Methotrexate + Adalimumab (6.4%) respectively. Another popular scheme was Leflunomide + Rituximab (20.9%), Leflunomide + Adalimumab (18.2%) and Leflunomide + Etanercept (11.8%).

When we analysed the correlation between ESR and medication, we observed that the lowest mean level is found in patients treated with Hydroxychloroquine + Rituximab and Methotrexate + Adalimumab, and the highest was recorded in subjects who received Hydroxychloroquine + Tocilizumab.

Regarding the classic inflammatory marker (CRP), the lowest mean level was recorded in patients treated with Methotrexate + Adalimumab, and the highest in subjects treated with Hydroxychloroquine + Tocilizumab.

Measurement of periodontal indexes revealed the lowest mean Quigley Hein index was in subjects under a combination of Sulfasalazine and Rituximab therapy, and the highest scores were for Leflunomid and Etanercept combination.

GI index mean was lowest in subjects under Methotrexate or Leflunomide and Adalimumab combination, on the other hand, the highest was observed in the Leflunomide or Methotrexate and Rituximab combination. The lowest mean level of PBI is observed in patients treated with Leflunomid + Etanercept, and the highest in patients treated with Leflunomid + Rituximab. Regarding another specific clinical periodontal marker, the mean CPITN level did not differ significantly depending on the combined synthetic and biological DMARDS treatment.

In our study, RF was registered in a positive proportion of 86.4%, and the correlation of rheumatoid factor positivity with the staging of rheumatoid arthritis showed that as the joint damage is in a more advanced stage, so does the probability of the presence of RF.

In a systematic review in 2016, Fuggle et al. revealed that there is an increased risk of bleeding on probing (BOP) in patients with RA compared to subjects without joint damage ($p = 0.05$), and in terms of oral hygiene parameters, the gingival index (GI) was significantly higher in level in RA compared to healthy controls; not the same was recorded in the plaque index analysis, another parameter of oral hygiene analysed in that study [19].

In 2015, Araújo et al. published a review of studies investigating the relationship between RA and periodontitis, in which articles were selected from 2012, including eight epidemiological studies, four periodontal intervention studies and five studies that investigated the role of inflammatory mediators in both diseases, highlighting that 21 of studies confirmed the association of the two entities, by statistical analysis, while 3 studies demonstrated an association by descriptive analysis [20].

Two studies from 2013, Bıyıkoğlu et al., and Erciyas et al., respectively, analysed the effect of non-surgical periodontal therapy on the DAS 28 score, both observing a reduction of this parameter, with values that remained stable

post-treatment [21, 22]. Moreover, Erciyas et al. also analysed other parameters such as ESR and CRP and noted that the changes were more prominent in the group with high disease activity compared to the group with low activity [22].

In our study, the modified values of the analysed oral and periodontal health indices were significantly correlated with stage III or IV of RA. Most likely, the motor restrictions encountered by these patients make it difficult to achieve adequate oral hygiene; the burden of the disease in general affecting the quality of life can be additional factors in the subsistence of a poor periodontal status.

The analysed data in our study show that as the rheumatic damage increases, the oral status is altered in direct proportion to all indices, but especially in terms of GI and PBI which are relevant oral indicators in case of an exacerbated systemic inflammatory status, a fact confirmed by Payne in 2015 [23]. Our study thus represents an opening to the clinical correlation between periodontal inflammatory status and the degree of rheumatic damage.

Several studies have shown that non-surgical periodontal treatment is able to reduce serum levels of TNF-α, IL-1β, IL-6, IL-10, MMP-8 and C-reactive protein and to modulate RA activity in patients with moderate to severe periodontitis [24, 25].

Modulation of T cell activation has provided another therapeutic target in RA with the use of abatacept, and inhibition of alveolar bone loss has suggested that treatment with RA may also improve the progression of periodontitis [26]; however, this is only an experimental study, without clinical data on human subjects available just yet.

In conclusion, there is no definitive data in human subjects to evaluate the effects of DMARDs on periodontitis due to the small number of patients studied and the lack of randomized, double-blind, placebo-controlled studies. The use of anti-TNF antibodies did not consistently prevent alveolar bone loss and generated aggravated or improved gingival inflammation, depending on the specific drug used. It is not clear whether these divergent results reflect differences in the structure of the studied anti-TNF studies. To date, the most impressive beneficial effect has been observed in inhibiting IL-6 related to tocilizumab, an IL-6 receptor antibody. Subsequent studies with tocilizumab, as well as observations with anti-IL-6 antibodies, may elucidate the importance of this cytokine in the pathogenesis of periodontitis.

The biological rationale for using DMARDS as a modulator of periodontitis expression in animals was confirmed by studies showing that mice deficient in the TN55-α p55 receptor developed less severe periodontal inflammation (reduced bone loss and a low inflammatory response) in response to inoculation with *A. actinomycetemcomitans* [27]. Using the same model of experimental periodontitis induced by *A. actinomycetemcomitans*, researchers found that antigen-induced arthritis exacerbated alveolar bone loss, while anti-TNF-α therapies improved the development of periodontitis [28].

To date, most research on the use of anti-cytokine therapies for periodontitis in humans has been limited to small clinical trials evaluating periodontal status in patients with rheumatoid arthritis under treatment. The findings from these studies tended to be inconsistent and somewhat confusing, probably due to the small number of patients with a variety of periodontal conditions, selected due to the primary inclusion criterion (anti-cytokine therapy for rheumatoid arthritis), different from the recruitment situation which was a targeted and deliberate one, in accordance with their periodontal status.

A study of three groups of patients (one with autoimmune diseases including RA who were not treated with anti-TNF-α therapy, the second with RA who received anti-TNF-α therapy and the healthy control group without autoimmune disease,

and no anti-TNF-α treatment) identified that patients with autoimmune disease who did not receive anti-TNF-α treatment had severe levels of gingival inflammation, bleeding on probing, higher mean probing depths and higher concentrations of TNF-α in the crevicular fluid compared to subjects in the other two groups [29]. This research has shown that patients with autoimmune disorders (including RA) have a much more severe periodontal inflammation than patients who do not suffer from autoimmune diseases, anti-TNF-α therapy reducing inflammation in periodontal tissues.

In our study, the combination of methotrexate and adalimumab had the lowest ESR and CRP values, consistent with multiple studies attesting to the systemic anti-inflammatory effect of methotrexate in particular [30, 31]. The combinations of leflunomide and adalimumab, as well as leflunomide with etanercept, recorded the most marked decrease in both rheumatic disease and oral health indices, results similar to those of McInnes and Schett in 2017 which identified that patients with rheumatoid arthritis who received anti-TNF-α treatment showed statistically significant improvements in probe depth, probe bleeding, and gingival inflammation compared to patients who did not receive anti-TNF-α therapy after non-surgical periodontal treatment [32].

The combination of leflunomide with rituximab or methotrexate with rituximab was associated in our study with the highest values of GI and PBI indices, data that coincides with similar studies in the literature [33]. Most likely these values are increased due to the inhibitory action of rituximab on CD20 B lymphocytes. When this drug binds to CD20 it triggers cellular death, which in time leads to almost complete depletion of peripheral B cells. Long-lived plasma cells that do not express this protein (CD20) are not directly affected by rituximab treatment, since this therapeutic agent only targets CD20 expressing cells.

Through our studies in which we analyzed the potential relation between the medication administered in rheumatoid arthritis and oral health indexes we could not confirm an effect on oral status of patients treated with conventional and synthetic DMARDS combination. An interesting finding is that patients treated with biologics had lower oral health indexes, thus a lower inflammation of the periodontal tissues. We could observe the beneficial effect of TNF-α inhibitors which although administered systemically have a local effect [15].

Adequate oral health measures should be part of the routine recommendations offered to RA patients. Adequate periodontal diagnosis by a periodontal specialist is necessary to determine the optimum course of treatment. Reducing the oral inflammatory contribution to the total inflammatory load as a result of the favourable outcome of periodontal treatment is an important desideratum. Maintaining the complete health of patients with RA must be a collaborative effort. This partnership dentist - rheumatologist will certainly influence the oral and overall health of these patients.

There is a strong association between RA and periodontitis. Interventions to prevent, reduce or treat periodontitis in arthritis patients will certainly promote better health status for these patients.

3. Periodontopathogenic bacteria in rheumatoid arthritis patients

Several studies have shown that periodontitis is more common in patients with active RA compared to healthy people; also, the prevalence of RA is higher in people with periodontitis compared to subjects without periodontitis [34]. In addition, the course of periodontal disease in patients with RA was more severe, regardless of age, sex, ethnicity, or smoking history [5].

Despite all the evidence supporting an association between these two diseases, the pathophysiological mechanisms have not yet been fully defined. In order to elucidate the clinical, biochemical and immunological interrelationship, it is necessary to perform longitudinal, prospective, large multi-center clinical trials to eliminate the risk of bias given by medication or associated pathology, oral hygiene, socioeconomic status, sex, age and vicious habits such as smoking.

Regarding the hypothesis of a causal link between periodontal disease and rheumatoid arthritis, where periodontitis is the determining factor, there are several theories in place.

The first one would be the release of extracellular traps by neutrophils (NET), in response to infection with *P. gingivalis*, structures characterized by active proteases and PAD. The concomitant action of these enzymes generates citrullinate epitopes and triggers the synthesis of ACPA. The production of citrullinate epitopes is accelerated by the synergistic action of gingipain and peptidilarginine deiminase of *P. gingivalis* (PPAD). Certain proteins from bacteria have the ability to mimic human proteins (bacteria enolase is similar to α-enolase in humans) on a molecular level and is thought to participate in the loss of immune tolerance to the organisms own molecules. Citrullinated epitopes in articular joints are the target of a secondary signal which causes increased generation of ACPA and rheumatoid factor, thus inducing immune complexes accumulation.

A second pathway would be neutrophil necrosis in the periodontal pocket, thus releasing danger-associated molecular patterns (DAMP) which circulate in the blood stream and exacerbate inflammation, both locally and systemically.

The third pathway is mediated by virulence factors expressed by *P. gingivalis*, such as lipopolysaccharides, fimbriae, gingipains, and lipoproteins, which are recognized by Toll-like receptors, protease-activated receptors, and/or NOD2 receptors on gingival and phagocytic epithelial cells. In response to pathogens, host cells release cytokines and chemokines that activate the complement system, RANKL, and promote T-helper cell differentiation, thus contributing to osteoclastogenesis [11].

PPAD-dependent disorder of immune tolerance caused by *P. gingivalis* can be considered the causal link between periodontal infection and RA; However, endogenous PADs are also important because they have very high values in chronic infections, such as periodontitis [35].

Recent findings make it clear that these two pathologies are intimately connected not only by similarities in pathogenic mechanisms and genetic and environmental risk factors, but also by data provided by cohort studies showing that periodontitis precedes the development of RA and that periodontal disease in individuals who develop RA at a later date correlates positively with ACPA levels; all of these are important arguments that support a causal interrelationship.

In this disease model, the inflamed periodontal tissue is the site where immune tolerance to citrulline epitopes is surpassed and ACPA production begins, this theory being verified in animal studies and is consistent with the paradigm according to which ACPAs are generated in mucosal surfaces, their formation preceding the clinical symptoms of rheumatic pathology for many years. In this case, periodontal pathogens can be considered direct determinants of autoimmune reactions, this being supported by case-control studies showing the generation of ACPAs and other mucosal surfaces such as the lungs and gastrointestinal tract, illustrating a heterogeneous picture of bacterial-host interactions within the human microbiome complexity.

In order to clarify this issue we conducted a study [36] on 19 patients with rheumatoid arthritis in order to identify bacterial DNA, by PCR analysis, in the subgingival dental plaque and serum in patients affected by rheumatoid arthritis

and periodontitis. The patients were diagnosed with refractory severe rheumatoid arthritis, in spite of intensive DMARDs treatment which included methotrexate, sulfasalazine, leflunomide and chloroquine. Patients who had other comorbidities were excluded from the study, as well as pregnant or nursing women, antibiotic therapy or periodontal treatment in the last 3 months prior to the study.

All patients were treated with DMARDs most of them also benefited from NSAID medication and low-dose steroids. The diagnosis of periodontitis was determined by measuring the depth of the periodontal pocket (PD) and the clinical loss of attachment (CAL).

The disease time course of rheumatoid arthritis was 8.71 (± 5.99) years, with a range of 0.5-20 years from the initial clinical diagnosis of rheumatoid arthritis. Chronic periodontitis was the most common type detected, whereas the aggressive form was present in only 5% of analyzed subjects, although the sample size for this study was small.

When we investigated the stage of periodontal disease, the most commonly represented for our study group was the severe stage (42.2%), whereas moderate (36.8%) and mild (21.1%) were present to a lesser degree. These percentages are similar to other studies [17]. The average overall depth of the pocket was 3.9 mm, however, taking into account the biggest depth of the pocket of each dental unit, the average was 4.2 mm. In terms of loss of attachment, the upper molars were the most affected (3.85 mm average).

The periodontopathogenic load was considerable for this group of patients, as nearly 100% of the subgingival samples were positive for bacteria and the venous blood samples in 84.2%. In subgingival samples *P. Intermedia* (100%), *T. denticola* (84.2%) and *P. gingivalis* (78.9%) were the most frequently observed, and in venous blood *P. Intermedia* 73.6% and *P. gingivalis* 42.1%.

The least common species detected was *A. actinomycetemcomitans* (15.7%). When we compare the two types of samples we can observe no significant statistical differences regarding *A. actinomycetemcomitans* and *P. gingivalis* between the samples, other hand, other analyzed species did show statistically significant differences.

In this study, only 19 patients were included due to the difficulty of finding patients who met the inclusion criteria. Patients with refractory rheumatoid arthritis treated with DMARDs were selected because this condition was necessary to obtain a serum sample with significant detectable characteristics. Most patients were female (84.2%), and was consistent with the information that rheumatoid arthritis affects women more than men [4].

It is justified to argue that the lower concentration of bacteria DNA in the venous blood is due to the renal filtration. Other authors found similar data by using a checkerboard DNA-DNA-hybridization set up and bacterial DNA was detected in 100% of analyzed serum samples thus implicating a continual aggression of oral pathogenic bacteria in joint disease [37].

In our study the most frequent bacterial species identified in venous blood were *P. gingivalis, T. denticola and P. intermedia,* the first two belonging to the red complex, and more often than not, correlated with a highly distructive periodontal disease pattern. On the other hand, *A. actinomycetemcomitans* which is thought to be mainly responsible for a more rapidly progressive type periodontitis, was less frequently detected. The reason could be that only one patient was affected. These data are consistent with previous reports.

The fact that *A. actinomycetemcomitans* and *P. gingivalis* did not show statistically significant differences between samples suggests that this could be a significant bacterial association for rheumatoid arthritis patients because the same bacteria species detected in serum were present also in bacterial plaque samples. On the

other hand, there were statistical differences between samples for *P. intermedia, T. forsythia, P. nigrescens* and *T. denticola*, suggesting a more minor role for these periodontal pathogens.

The tooth associated microflora has been extensively studied. The presence of *Porphyromonas gingivalis, Tannerella forsythia, Aggregatibacter actinomycetemcomitans* in the gingival sulcus poses an increased risk for developement and severity of periodontitis. Healthy versus diseased periodontal sites are different in terms of microbiological composition. The healthy sulcus has a lower bacterial load and also less morphological types, whereas the periodontal pocket is a complex microenvironment with an abundance of microorganisms that are mostly anaerobic gram-negative periodontopathogens [38].

Another interesting result of our study is the fact that all bacterial serum positive patients were also positive for the same bacteria in the subgingival plaque, thus proving a direct link to the oral cavity. On a similar note, some studies in the literature discovered antibodies against *P. intermedia* in periodontal tissues and in the synovium of subjects with rheumatoid arthritis. Moreover, the induction of proinflammatory cytokines in the synovial tissue of rheumatoid arthritis subjects is exacerbated by elevated heat shock protein 70 expressions precipitated by specific stress stimulating factors [39]. This confirms our results which place *P. intermedia* as the most frequently identified bacteria in rheumatoid arthritis subjects.

Whole-genome shotgun (WGS) sequencing is a newer technique that analyzes bacteria genomes with important roles in a metagenomic sample. Through this method a more global, complex image of the microbial ecosystem is obtained because it examines the metabolic pathways and the complete set of genes pertaining to the community.

A recent study determined that species of *Prevotella* (microorganisms of oral origin) are increased in the gut microbiome of rheumatoid arthritis subjects [40]. These results are sustained by another study performed on patients in preclinical rheumatoid arthritis stages that reported high numbers of *Prevotella spp* in these patients [41]. Thus colonization by oral microorganisms of the gut could be linked to the pathogenesis of rheumatic diseases.

Metagenomic studies are an important research direction that could establish other links in the periodontitis-rheumatoid arthritis binome, and have the potential to better determine the microbial diversity and ecology in these subjects.

Considering the presented data it is fair to articulate an important role of oral pathogens DNA in the pathogenesis of rheumatic diseases. The migration of DNA from periodontal pockets to the joints could be by means of the free bacterial DNA. This information can be valuable for future studies to elucidate whether periodontal pathogenic DNA might be a possible trigger for rheumatoid arthritis development.

4. Future research possibilities in the rheumatoid arthritis-periodontitis interface

Host response modulation therapy is a highly researched topic in the scientific literature, and more specifically, when referring to the management of periodontal disease, a number of potential drugs have been considered for treatment. The first studies on this topic date back 30 years ago and they analyzed the intake of nonsteroidal anti-inflammatory drugs for the minimization of alveolar bone loss. Due to the fact that they were prescribed for long periods of time, important undesirable side effects were associated with their administration, and thus precluding their use as adjunctive therapy for periodontitis; in other words, the associated risks far outweigh any potential benefits in reducing alveolar bone resorption.

In the 1990s, a new wave of research investigated the use of tetracycline compounds, specifically doxycycline, after identifying its efficacy as an inhibitor of matrix metalloproteinases. Randomized controlled clinical trials have confirmed a benefit of using subantimicrobial doses (20 mg twice daily for 3 months) as an adjunct to conventional non-surgical treatment, with no evidence of undesirable side effects. To date, this dose of doxycycline is the only drug therapy widely available, authorized as a host modulating agent for use in the treatment of periodontal disease. However, not all studies have shown the same clear benefit as seen in large-scale clinical trials, and there are still uncertainties about the category of patients for whom such treatment would provide feasible results, and can be anticipated in routine periodontal practice [42].

Anti-cytokine therapies have a proven efficacy in the management of rheumatoid arthritis and, given the similarities between the pathogenesis of rheumatoid arthritis and periodontitis, researchers' interest in anti-cytokine therapies as potential modulators of the host response in the treatment of periodontitis is justified. However, there are concerns associated with their use due to well-documented side effects, such as an increased risk of infection and malignancy [43]. In addition, cytokines function in complex cellular and molecular networks that integrate aspects of innate and adaptive immunity that are still challenging to assess in their complexity.

Similar to other autoimmune and chronic inflammatory conditions, our knowledge of all cytokine functions in periodontitis is far from exhaustive, and simple inhibition of a certain cytokine may not determine a clinically significant impact on the researched pathological condition. This is due to the fact that a great deal of cytokines and biomolecules exert a similar effect on the cells they interact with, thus it is possible that inhibition of a certain cytokine could have little to no detectable influence on a pathological condition. This is by consequence of other cytokines which have a similar function to the one that was repressed. In addition, even though animal models may suggest certain anti-cytokine drugs that could ameliorate, or even amend, the course of a disease such as rheumatoid arthritis, they cannot predict exactly whether the same efficacy can be obtained in human or individual patient studies.

In the treatment of rheumatoid arthritis, inhibition of TNF-α with antagonist therapies plus methotrexate has clearly demonstrated clinical improvements, due to the fact that this molecule is of major importance in the pathogenesis of the disease. Moreover, anti-TNF-α therapy in patients with rheumatoid arthritis results in a reduction of other pro-inflammatory mediators, such as IL-1β and IL-6, leading to an improvement of the anti-inflammatory effect [32]. Even so, the use of these therapies does not lead to complete eradication of the disease, and success factors are assessed using composite scales that take into account not only the improvement quantified in percentage in the clinical signs and symptoms of the disease, but also the high cost and high risk of significant side effects.

The method of administration (typically repeated subcutaneous injections or intravenous infusions) is another limiting factor; however, it is possible that future generations of anti-TNF-α agents (possibly even locally released) may have a much higher impact on the treatment of periodontitis.

Compounds with small molecules, for example histone deacetylase inhibitors, could potentially successfully manage certain pathological conditions that determine bone resorption. Considering the fact that they have an inhibitory effect on the activity of osteoclasts they could be coupled with anti-inflammatory drugs for the minimization of inflammation and osseous resorption. Another area of interest is the advancement of synthetically produced specific deacetylase inhibitors targeting the histone diacetylases that are implicated in the dysfunction process [44].

On the other hand, the potential side-effects on other cellular processes are not to be ignored and supplementary studies characterizing the risk-benefit ratio are paramount. Another potentially confounding or even aggravating factor may be the difference in mechanism of action of biological therapies in animal versus human subjects which could have unfortunate consequences when applied for the first time. In spite of all this, these compounds are currently being evaluated in early-stage clinical trials as a treatment plan in neoplasms and show promising preliminary results in terms of effectiveness and toleration [45].

A newly emerging class of drugs that shows great promise in the adjunctive treatment of periodontal disease is pro-resolution lipid mediators. A major benefit of these endogenous compounds is that they are generated as a physiological response to inflammation (resolution agonists), contrary to inhibitors of inflammation that may imperil host defense [46]. The development of drugs that mimic the actions of endogenous mediators that lead to the resolution of inflammation could be useful in the treatment of a number of chronic inflammatory diseases, including periodontitis; obviously, efforts to demonstrate their safety and effectiveness will be commensurate.

Therefore, the immunomodulatory properties of a number of molecules and classes of drugs are being investigated, with the precise purpose of evaluating the applicability in the treatment of periodontal disease. The challenge at hand that still remains is to capitalize on the information gained from fundamental studies and animal model experiments in order to promote the development and evaluation of these compounds as novel therapeutic options. Furthermore, assessment of the risk/benefit ratio driven by large scale clinical use, taking into account the potential diversity in the response profile in-between subjects, interactions with other medication and potential adverse effects is imperative. Nonetheless, it is highly possible that in the future a new series of modular anti-inflammatory and pro-resolving therapies will be identified; these therapeutic agents could have direct relevance as adjuvants in the treatment of periodontal disease.

5. Conclusions

Significant evidence suggests that citrullination may bind periodontal disease to rheumatoid arthritis. Genetic factors drive host responses to chronic diseases with complex pathogenesis. In the future, more effective therapeutic approaches will include multiple synergistic therapies to modulate the host response, combined with treatments that target microbial etiology. Further studies are needed to better understand these mechanisms and help maintain overall health, with oral health parameters requiring close monitoring in patients with RA.

Given the similarities between aspects of the pathogenesis of periodontitis and rheumatoid arthritis, it is relevant that in the periodontology research community there is a great deal of interest for optimizing the treatment options applicable in rheumatoid arthritis patients. Even though impaired immune tolerance and introduction of symptoms in rheumatoid arthritis have yet to be fully comprehended, it is evident that concerning the pathogenesis of this disease the inflammatory cascade is the leading actor from start to finish; beginning with the initiation of autoimmunity, to the subsequent synovial localization, and culminating in the joint and bone tissue destruction.

Interventions to improve oral pathology can have direct and indirect systemic benefits. Considerations which must be taken into account include the patient's ability to maintain adequate oral hygiene, xerostomia and associated complications due to drug intake or disease course, the patient's susceptibility to infections, alterations in hemostasis, and drug mechanism of action and interactions.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Monsarrat P, Blaizot A, Kemoun P, Ravaud P, Nabet C, Sixou M, et al. Clinical research activity in periodontalmedicine: a systematic mapping of trial registers. J Clin Periodontol. 2016;43(5):390-400. doi:10.1111/jcpe.12534.

[2] Loos BG. Periodontal medicine: work in progress! J Clin Periodontol. 2016;43(6):470-1. doi:10.1111/jcpe.12550

[3] Zenobia C, Hajishengallis G. Basic biology and role of interleukin-17 in immunity and inflammation. Periodontology 2000. 2015 Oct 1;69(1):142-59.

[4] Catrina AI, Svensson CI, Malmström V, Schett G, Klareskog L. Mechanisms leading from systemic autoimmunity to joint-specific disease in rheumatoid arthritis. Nature Reviews Rheumatology. 2017 Feb;13(2):79.

[5] Mikuls TR, Payne JB, Deane KD, Thiele GM. Autoimmunity of the lung and oral mucosa in a multisystem inflammatory disease: The spark that lights the fire in rheumatoid arthritis?. Journal of Allergy and Clinical Immunology. 2016 Jan 1;137(1):28-34.

[6] Rosenbaum JT, Asquith MJ. The microbiome: a revolution in treatment for rheumatic diseases?. Current rheumatology reports. 2016 Oct 1;18(10):62.

[7] Montgomery AB, Kopec J, Shrestha L, Thezenas ML, Burgess-Brown NA, Fischer R, Yue WW, Venables PJ. Crystal structure of Porphyromonas gingivalis peptidylarginine deiminase: implications for autoimmunity in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2016 Jun 1;75(6):1255-61

[8] Gawron K, Montgomery A, Łazarz-Bartyzel K, Bereta G, Chomyszyn-Gajewska M, Venables P, Potempa J. Porphyromonas gingivalis peptidyl arginine deiminase: A Unique bacterial PAD with implications for periodontal disease and rheumatoid Arthritis. InProtein Deimination in Human Health and Disease 2017 (pp. 99-135). Springer, Cham.

[9] Muller S, Radic M. Citrullinated autoantigens: from diagnostic markers to pathogenetic mechanisms. Clinical reviews in allergy & immunology. 2015 Oct 1;49(2):232-9.

[10] Trouw LA, Rispens T, Toes RE. Beyond citrullination: other post-translational protein modifications in rheumatoid arthritis. Nature Reviews Rheumatology. 2017 Jun;13(6):331.

[11] Potempa J, Mydel P, Koziel J. The case for periodontitis in the pathogenesis of rheumatoid arthritis. Nature Reviews Rheumatology. 2017 Oct;13(10):606.

[12] Schmickler J, Rupprecht A, Patschan S, Patschan D, Müller GA, Haak R, Mausberg RF, Schmalz G, Kottmann T, Ziebolz D. Cross-Sectional Evaluation of Periodontal Status and Microbiologic and Rheumatoid Parameters in a Large Cohort of Patients With Rheumatoid Arthritis. Journal of periodontology. 2017 Apr;88(4):368-79.

[13] Conigliaro P, Triggianese P, De Martino E, Fonti GL, Chimenti MS, Sunzini F, Viola A, Canofari C, Perricone R. Challenges in the treatment of rheumatoid arthritis. Autoimmunity reviews. 2019 Jul 1;18(7):706-13.

[14] Kerschbaumer, A., Sepriano, A., Smolen, J.S., van der Heijde, D., Dougados, M., van Vollenhoven, R., McInnes, I.B., Bijlsma, J.W., Burmester, G.R., de Wit, M. and Falzon, L., 2020. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019

update of the EULAR recommendations for management of rheumatoid arthritis. Annals of the Rheumatic Diseases, 79(6), pp.744-759.

[15] Martu MA, Rezus E, Popa C, Solomon SM, Luchian I, Pendefunda AC, Sioustis I, Anton D, Martu S, Foia L. Correlations between systemic therapy with conventional (synthetic) and biological DMARDS, rheumatoid arthritis and periodontal indices of chronic periodontitis. Romanian Journal of Oral Rehabilitation. 2018 Oct 1;10(4).

[16] Eriksson K, Fei G, Lundmark A, Benchimol D, Lee L, Hu YO, Kats A, Saevarsdottir S, Catrina AI, Klinge B, Andersson AF. Periodontal health and oral microbiota in patients with rheumatoid arthritis. Journal of clinical medicine. 2019 May;8(5):630.

[17] Rodríguez-Lozano B, González-Febles J, Garnier-Rodríguez JL, Dadlani S, Bustabad-Reyes S, Sanz M, Sánchez-Alonso F, Sánchez-Piedra C, González-Dávila E, Díaz-González F. Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients: a case–control study. Arthritis research & therapy. 2019 Dec;21(1):1-2.

[18] Schmickler J, Rupprecht A, Patschan S, Patschan D, Müller GA, Haak R, Mausberg RF, Schmalz G, Kottmann T, Ziebolz D. Cross-sectional evaluation of periodontal status and microbiologic and rheumatoid parameters in a large cohort of patients with rheumatoid arthritis. Journal of periodontology. 2017 Apr;88(4):368-79.

[19] Fuggle NR, Smith TO, Kaul A, Sofat N. Hand to mouth: a systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. Frontiers in immunology. 2016 Mar 2;7:80.

[20] Araújo VM, Melo IM, Lima V. Relationship between periodontitis and rheumatoid arthritis: review of the literature. Mediators of inflammation. 2015;2015.

[21] Bıyıkoğlu B, Buduneli N, Aksu K, Nalbantsoy A, Lappin DF, Evrenosoğlu E, Kinane DF. Periodontal therapy in chronic periodontitis lowers gingival crevicular fluid interleukin-1beta and DAS28 in rheumatoid arthritis patients. Rheumatology international. 2013 Oct 1;33(10):2607-16.

[22] Erciyas K, Sezer U, Üstün K, Pehlivan Y, Kısacık B, Şenyurt SZ, Tarakçıoğlu M, Onat AM. Effects of periodontal therapy on disease activity and systemic inflammation in rheumatoid arthritis patients. Oral diseases. 2013 May;19(4):394-400.

[23] Payne JB, Golub LM, Thiele GM, Mikuls TR. The link between periodontitis and rheumatoid arthritis: a periodontist's perspective. Current oral health reports. 2015 Mar 1;2(1):20-9.

[24] Kirchner A, Jäger J, Krohn-Grimberghe B, Patschan S, Kottmann T, Schmalz G, Mausberg RF, Haak R, Ziebolz D. Active matrix metalloproteinase-8 and periodontal bacteria depending on periodontal status in patients with rheumatoid arthritis. Journal of periodontal research. 2017 Aug;52(4):745-54.

[25] Cosgarea R, Tristiu R, Dumitru RB, Arweiler NB, Rednic S, Sirbu CI, Lascu L, Sculean A, Eick S. Effects of non-surgical periodontal therapy on periodontal laboratory and clinical data as well as on disease activity in patients with rheumatoid arthritis. Clinical oral investigations. 2018 Mar 27:1-1.

[26] Weitzmann MN, Ofotokun I. Physiological and pathophysiological bone turnover—role of the immune system. Nature Reviews Endocrinology. 2016 Sep;12(9):518.

[27] Garlet GP, Cardoso CR, Campanelli AP, Ferreira BR,

Avila-Campos MJ, Cunha FQ, Silva JS. The dual role of p55 tumour necrosis factor-α receptor in Actinobacillus actinomycetemcomitans-induced experimental periodontitis: host protection and tissue destruction. Clinical & Experimental Immunology. 2007 Jan;147(1):128-38.

[28] Corrêa MG, Sacchetti SB, Ribeiro FV, Pimentel SP, Casarin RC, Cirano FR, Casati MZ. Periodontitis increases rheumatic factor serum levels and citrullinated proteins in gingival tissues and alter cytokine balance in arthritic rats. PloS one. 2017 Mar 30;12(3):e0174442.

[29] Mayer Y, Elimelech R, Balbir-Gurman A, Braun-Moscovici Y, Machtei EE. Periodontal condition of patients with autoimmune diseases and the effect of anti-tumor necrosis factor-α therapy. Journal of periodontology. 2013 Feb;84(2):136-42.

[30] Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, Bijlsma JW, Burmester GR, Scholte-Voshaar M. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Annals of the rheumatic diseases. 2017 Jun 1;76(6):1101-36.

[31] Orr CK, Najm A, Young F, McGarry T, Biniecka M, Fearon U, Veale DJ. The Utility and Limitations of CRP, ESR and DAS28-CRP in Appraising Disease Activity in Rheumatoid Arthritis. Frontiers in medicine. 2018;5.

[32] McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. The Lancet. 2017 Jun 10;389(10086):2328-37.

[33] Ziebolz D, Rupprecht A, Schmickler J, Bothmann L, Krämer J, Patschan D, Müller GA, Mausberg RF, Schmidt J, Schmalz G, Patschan S. Association of different immunosuppressive medications with periodontal condition in patients with rheumatoid arthritis–results from a cross-sectional study. Journal of periodontology. 2018 May 22.

[34] Eriksson K, Nise L, Kats A, Luttropp E, Catrina AI, Askling J, Jansson L, Alfredsson L, Klareskog L, Lundberg K, Yucel-Lindberg T. Prevalence of periodontitis in patients with established rheumatoid arthritis: a Swedish population based case-control study. PLoS One. 2016 May 20;11(5): e0155956.

[35] Shimada A, Kobayashi T, Ito S, Okada M, Murasawa A, Nakazono K, Yoshie H. Expression of anti-Porphyromonas gingivalis peptidylarginine deiminase immunoglobulin G and peptidylarginine deiminase-4 in patients with rheumatoid arthritis and periodontitis. Journal of periodontal research. 2016 Feb 1;51(1):103-11.

[36] Martu MA, Solomon SM, Sufaru IG, Jelihovschi I, Martu S, Rezus E, Surdu AE, Onea RM, Grecu GP, Foia L. Study on the prevalence of periodontopathogenic bacteria in serum and subgingival bacterial plaque in patients with rheumatoid arthritis. Rev. Chim. (Bucharest). 2017 Aug 1;68(8):1946-9.

[37] Moen K, Brun JG, Valen M, Skartveit L, Eribe EK, Olsen I, Jonsson R. Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. Clin Exp Rheumatol. 2006 Dec;24(6):656-3.

[38] Curtis MA, Diaz PI, Van Dyke TE. The role of the microbiota in periodontal disease. Periodontology 2000. 2020 Jun;83(1):14-25.

[39] Schenkein HA, Papapanou PN, Genco R, Sanz M. Mechanisms underlying the association between

periodontitis and atherosclerotic disease. Periodontology 2000. 2020 Jun;83(1):90-106.

[40] Kishikawa T, Maeda Y, Nii T, Motooka D, Matsumoto Y, Matsushita M, Matsuoka H, Yoshimura M, Kawada S, Teshigawara S, Oguro E. Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population. Annals of the rheumatic diseases. 2020 Jan 1;79(1):103-11.

[41] Wells PM, Adebayo AS, Freidin MB, Finckh A, Strowig T, Lesker TR, Alpizar-Rodriguez D, Gilbert B, Kirkham B, Cope AP, Steves CJ. A polygenic risk score for rheumatoid arthritis sheds light on the Prevotella association. MedRxiv. 2019 Jan 1.

[42] Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nature Reviews Disease Primers. 2017 Jun 22;3:17038

[43] Meyle J, Dommisch H, Groeger S, Giacaman RA, Costalonga M, Herzberg M. The innate host response in caries and periodontitis. Journal of clinical periodontology. 2017 Dec;44(12):1215-25.

[44] Grabiec AM, Potempa J. Epigenetic regulation in bacterial infections: targeting histone deacetylases. Critical reviews in microbiology. 2018 May 4;44(3):336-50.

[45] Cappelli LC, Shah AA. The relationships between cancer and autoimmune rheumatic diseases. Best Practice & Research Clinical Rheumatology. 2020 Feb 3:101472.

[46] Van Dyke TE, Sima C. Understanding resolution of inflammation in periodontal diseases: Is chronic inflammatory periodontitis a failure to resolve?. Periodontology 2000. 2020 Feb;82(1):205-13.