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Review Article

Relation of Rheumatoid Arthritis and Periodontal Disease

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Abstract

Periodontal disease and rheumatoid arthritis are both inflammatory diseases. It is well known that there are associations between periodontitis and other systematic diseases like cardiovascular disease, diabetes mellitus and alterations during pregnancy. This review analyses the literature available dealing with the relationship between periodontal disease and rheumatoid arthritis.

Periodontitis is an infection disease which causes inflammation. Porphyromonas gingivalis is the most common pathogen connected with periodontitis. This bacterium has the peculiarity of being able to produce peptidylarginine deiminase, a proteolytic enzyme with an important role in inflammatory diseases like rheumatoid arthritis.

Furthermore, several case-control studies related the clinical activity and biochemical markers levels of rheumatoid arthritis with non-surgical periodontal treatment. The studies confirm that the non-surgical treatment of periodontitis improves both the biomarkers and the clinical situation of rheumatoid arthritis. In addition to this, the fact that antibiotics, such as minocycline, have been successfully used for the treatment of rheumatoid arthritis for many years could explain the relationship of rheumatoid arthritis with infection diseases like periodontal disease.

The relationship between rheumatoid arthritis and periodontal disease seems clear, but it is necessary to carry out more studies with a greater number of case-controls and a longer period of follow-up research.

ABBREVIATIONS

RA: Rheumatoid Arthritis; PD: Periodontal Disease; CAL: Clinical Attachment; PAD: Peptidylargininie Deiminase; PPAD: Porphyromonas Gingivalis Peptidylarginine Deiminase; RF: Rheumatoid Factor; DAS28: Disease Activity Score; ESR: Erythrocyte Sedimentation Rate; IL-6: Interleukin-6; CRP: C-Reactive Protei;, TNF-A: Tumour Necrosis Factor-A; DNA: Deoxyribonucleic Acid.

INTRODUCTION

Periodontal Disease (PD) is one of the most frequent oral disorders and the most common causes of tooth loss in elderly patients. The chronic inflammation of PD with the constant release of inflammatory mediators may be a risk factor for the development of systemic inflammatory disease [1]. It is well known, backed up by a considerable body of evidence, that there are associations between PD and diabetes mellitus, cardiovascular disease, respiratory disease, obesity and some alterations during pregnancy [2]. Furthermore, there is considered to be a relationship between PD and Rheumatoid Arthritis.

Rheumatoid Arthritis (RA) is an autoimmune disease leading to chronic synovial inflammation and destruction of the cartilage and bone, particularly affecting the small joints of the hands and feet and resulting in different degrees of deformity and functional disability [3, 4].

In this paper, we are going to analyse current literature relating to periodontal disease as a factor for RA, reviewing the periodontal status of patients with RA, the effect of oral micro biota on RA disease and the importance of the peptidylargininie deiminase enzyme on the activity of RA [5]. Finally, we will analyse the effect of non-surgical periodontal treatment on RA activity, measuring its biochemical biomarkers.

The oral microbiota in RA

The human mouth is the second largest bacterial community of the body, after the lower gastrointestinal tract. Scientists have identified over 700 oral cavity bacterial species [6]. The oral microbiota is involved in the etiology of PD, and it may be a contributory factor in the etiopathogeny of some chronic inflammatory diseases, such as RA [7]. Periodontal pathogens can enter the systematic circulation as a result of bacteremia after brushing the teeth, chewing, and after dental treatment [8, 9].

Several studies suggested that a higher prevalence of severe periodontitis and tooth loss caused by PD correlates with RA activity.

Is it now generally accepted that chronic periodontitis is initiated by the colonisation of dental plaque by several pathogenic bacteria: Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola and Tannerella forsythia [10]. The DNA of these bacteria has been detected in the synovial fluid of patients with RA [11,12].

The Porphyromonas gingivalis, the most common pathogen of PD, is of particular interest in RA because it has the capacity to produce and secrete peptidylarginine deiminase (PAD), an enzyme responsible for the citrullination of endogenous peptides, human α-enolase peptides and fibrinogen [13]. Therefore, PAD is the major candidate for explaining the possibility that PD is an etiogenic factor for AR [14].

The porphyromonas peptidylarginine deiminase (PAD)

Peptidylarginine deiminase (PAD) is a proteolytic enzyme, also known as gingipains, produced by P. Gingivalis, which contributes to local tissue destruction and direct apoptosis of gingival cells. This enzyme is also called Porphyromonas gingivalis peptidylarginine deiminase (PPAD) because Porphyromonas Gingivalis is the only known bacterium that can produce the enzyme [4].

This enzyme converts arginine to citrulline, resulting in a structural protein modification. This structural modification is believed to generate a new range of antigens including citrullinated filaggrin, vimentin, collagen and enolase [4].

Protein citrullination is carried out by peptidyl-arginine deiminases (PAD), while the activity of mammalian and human PAD enzymes is dependent on high concentrations of calcium. Five different PADs exist, and have been identified in the human body, found in the epidermis, hair follicles, hematopoietic cells, muscles and brain. PPAD differs significantly from human PAD because it is active at a higher pH and does not require calcium for activity. PPAD also citrullinates C-terminal arginine residues and de-iminates free arginine, while PADs do not do this [15, 16].

Koziel et al. [15], describe the sequence of pathogenesis of PPAD as inflammation of the gums caused by periodontal infection which releases human intracellular PAD, resulting in the citrullination of proteins in gums by Porphyromonas Gingivalis and activating the production of antibodies against citrullinated proteins, resulting in inflammation of the joints and a new release of human intracellular PAD, producing citrullinations of proteins in the joints and chronic inflammation as RA.

Periodontal status of rheumatoid arthritis patients

There are several studies about clinical attachment (CAL) loss in patients, with or without rheumatoid arthritis. Gariband Qaradaxi [17], in their case-control study involving 100 patients, recorded a result of more than 1 mm of difference in CAL between RA patients and non-RA patients. Pischon et al. [18], reported similar results, getting a major CAL, 1.03 mm, in RA patients. All these suggest that clinical attachment loss is more common in patients with RA than patients without RA [19].

Some studies examined also the extent of tooth loss in patients with RA or without RA. Kabayashi et al. [20], studied 100 patients with RA and 100 patients without RA. The group with RA had 3.3 more teeth missing than the control group. Kasser et al. [21], Garib and Qaradaxi [17] and Joseph et al. [22], got similar results. All this indicates that the extent of tooth loss is greater in patients with RA than in patients without RA [19].

The effect of conservative periodontal treatment in the biochemical markers in RA

The non-surgical periodontal treatment included procedures involving oral hygiene, supragingival cleaning (ultrasound) and root rasping and scaling, or curettage. There are several studies that related the effect of non-surgical treatment periodontal treatment and the RA disease activity [23-28]. These investigations are case-control studies and evaluate the biochemical markers of RA before and after conservative periodontal treatment. The biochemical markers studied are rheumatoid factor (RF), disease activity score (DAS28), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), C-reactive protein (CRP) and tumour necrosis factor.

The study observation periods ranged from 6 weeks to 6 months, which is considered to be short, but long enough to observe clinical change with regard to reduction in inflammation, infection and depth socket. All the studies described employed an appropriate method and control groups, but suffered from low sample sizes and short study duration.

Rheumatoid factor (RF): RF has been used for a long time as a diagnostic marker for RA. However, it is not a specific antibody, and it is not positive in 15% of the patients with RA [19,29,30]. Some studies investigating the levels of RF in PD and in RA and reported statistically significantly higher levels of RF in patients with both diseases. Statistically, non-surgical periodontal treatment reduces the RF levels significantly [18,29,31].

Disease activity score (DAS28): Some studies showed a reduction in DAS score following non-surgical periodontal treatment in patients with AR, but it did not seem statistically significant [23,25,27,29]. Other studies [32] reported a significant reduction in DAS28 following conservative periodontal treatment after 5 months of treatment.

C-reactive protein (CRP): This is an acute-phase protein synthesized by the liver which increases its level of serum in inflammatory disease [19]. There are several studies that evaluated CRP in patients with PD. Ortiz et al.[25], Okada et al.

[24], Biyikoğlu*et* al. [31], Pischon et al. [18], and Joseph et al. [22], did not show a statistically significant difference in CRP between patients with PD and patients without PD.

Erythrocyte sedimentation rate (ESR): This is a good marker for the presence of systemic inflammation and is useful for RA. There are four studies in the available literature evaluating the ESR level in AR following non-surgical periodontal treatment. Three of them reported a decreased level of ESR following periodontal treatment [23, 25-27, 29].

Interleukin-6 (IL-6): IL-6 is an inflammatory cytokine present in increased levels in PD and RA. Increased levels occur in the case of patients suffering AR and PD. A study reported decreased IL-6 levels after non-surgical periodontal treatment, but this was not significant [24,29]. Another study reports that IL-6 was higher in patients with active PD than in patients without PD [31].

Tumour Necrosis Factor-α (TNF-α): TNF-α is another inflammatory cytokine associated with chronic inflammatory disorders. Mirrielees et al. [33], did not find a correlation between TNF-α in RA patients with or without PD. There are no studies relating conservative periodontal treatment and TNF-α in RA patients.

ANTIBIOTICS FOR THE TREATMENT OF AR

Since the 1930s, RA has been treated with antibiotics. The first antibiotic used was sulphonamide. Then in the 60s tetracycline was used. A few years ago, randomised trials were carried out to investigate the use of minocycline for the treatment of RA [34]. This means that to date there have been four double blind, randomized clinical studies published regarding the use of minocycline for the treatment of RA. All of them compared the administration of minocycline and a placebo, and they had a duration of between 1 and 2 years. The four trials showed that minocycline is efficacious in the treatment of RA [34-38].

Levofloxacin is used in the treatment of infections caused by periodontal bacteria and facultative anaerobic bacteria [34]. Ogrendik [39], in a randomized double-blind study with 76 patients with persistently active RA, achieved a more marked improvement in patients with conventional treatment (methotrexate) plus levofloxacin than with conventional treatment and placebo.

Macrolide antibiotics have also been studied. Macrolides are protein synthesis inhibitors and are used to treat infections caused by gram-negative anaerobic bacteria [34]. Saviola et al. [40], compared the efficacy of adding (or not adding) clarithromycin over a period of 4 weeks to the conventional treatment (methotrexate and methylprednisolone) for active RA. The trial showed that the clarithromycin cycle was efficacious in inducing the remission of the disease.

In his systematic review concerning antibiotics for the treatment of RA, Ogrendik proposes that the efficacy of the antibiotics on treatment in RA suggest the implication of microorganisms such as periodontal bacteria in the pathogenesis of RA [34].

CONCLUSION

Numerous case-control studies have demonstrated an association between RA and PD. All these studies had appropriate control groups and adequate methods, but suffered from low sample sizes and short study duration. It seems that attachment loss and an increase in tooth loss are more pronounced in patients with RA than in patients without RA. The studies confirm that the non-surgical treatment of PD improves the biomarkers of RA, and the activity and clinical situation of RA. As for antibiotics, however, it seems that the studies confirm the efficacy of these drugs in the treatment of RA, and may correlate the relationship between RA and microorganism. Both inflammatory diseases, PD and RA, are related but more studies are needed with a greater number of case-controls and a minimum of twelve months follow-up.

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