REVIEW ARTICLE

Associations between marginal periodontitis and rheumatoid arthritis

Michal Straka [1], Michaela Trapezanlidis [2], Peter Dzupa [3], Rastislav Pijak [4]

1 Department of Stomatology, Slovak Medical University in Bratislava, Slovakia
2 Private practice, Bratislava, Slovakia
3 Private practice, Cadca, Slovakia
4 First Internal Clinic, FNsP, Bratislava, Slovakia

Correspondence to: Michal Straka, MD., PhD.
Department of Stomatology, Slovak Medical University in Bratislava,
Limbová 14, Bratislava, 833 03, Slovakia.
tel: +421 2 59370851 ; e-mail: michal.straka@szu.sk

Submitted: 2011-11-10 Accepted: 2012-01-08 Published online: 2012-03-10

Key words: **periodontitis; infection; rheumatoid arthritis; treatment**

Neuroendocrinol Lett 2012; **33**(1):16–20 **PMID:** 22467106 NEL330112R02

Abstract

Chronic destructive periodontitis is no longer considered to be just a local inflammatory process afflicting the periodontal tissues, but a systemic infection. Bacteria, their products and various pro-inflammatory cells and substances can penetrate into the blood stream and infect distant organs and structures. Periodontitis and rheumatoid arthritis indicate several common histo-pathological correlations, as the destroyed osseous tissues and cartilages are permanently washed with inflammatory fluid full of proteolytic and osteolytic substances. Although exact causal and molecular associations between both diseases have not been explained yet, there are some common etiopathogenic correlations that can have influence on relationship between both diseases. Among these factors belong: a positive finding of common genes, genetic polymorphisms and hyper-inflammatory types of some immune competent cells and molecules, common cytokine profiles and increased concentrations of pro-inflammatory mediators in periodontal and joint structures. Periodontitis and some periodontal pathogens can influence various auto-immune reactions connected with rheumatoid arthritis (RF, anti-CCP). Possible causal associations are indicated in some studies dealing with treatment of RA, when a beneficiary effect of RA treatment led to improvement of some periodontal parameters. This relationship works both ways; the periodontal therapy had positive influence on some markers of rheumatoid arthritis. This provides sufficient theoretic evidence to perform professional and personal oral hygiene in a more active way.

INTRODUCTION

Our current knowledge permanently confirms destructive marginal periodontitis to be a source of a systemic infection when local chronic inflammation penetrates into the blood stream and infects the whole organism. This can initiate or accelerate the destructive inflammatory process in distant tissues and organs mainly in susceptible individuals. Periodontitis (PD) is no longer considered to be just a local chronic asymptomatic inflammation of the periodontal tissues. Instead it is a serious inflammatory process with a possible impact on the whole organism. Periodontal pockets caused by osteolysis are difficult to destroy during common dental hygiene and are packed with anaerobic bacteria, LPS-endotoxins and pro-inflammatory mediators. The walls of periodontal pockets are covered with a subgingival bacterial biofilm, 1 mg of which can contain from 10^8 up to

10^9 bacteria (Loeshe 1994). These bacteria, their products and pro-inflammatory mediators can penetrate into the blood stream then colonize and attack other tissues and structures in susceptible subjects.

Rheumatoid arthritis is today considered to be an immunological disease accompanied by formation of auto-antibodies against one's own IgM and IgA immunoglobulins. The disease is characterized by increased concentrations of various pro-inflammatory substances and immunity-supporting cells, formation of synovial hyperplasia, deposition of fibrin in joints, accumulation of inflammatory cells leading to destruction of joint cartilage together with destruction of joint structure and function. Results of various studies have confirmed several common pathological, cellular and molecular characteristics of chronic periodontal and synovial inflammation (Smolik *et al.* 2009; Kobayashi *et al.* 2010).

EPIDEMIOLOGY AND STATISTICS OF MUTUAL ASSOCIATIONS

From 0.5 to 1% of the world population is afflicted with rheumatoid arthritis (RA), whilst the incidence of RA in patients with periodontitis is 3.95%. This indicates that periodontitis is, apart from other etiological factors, an independent risk factor of RA (Berthelot *et al.* 2010). Some studies have confirmed twice the occurrence of periodontitis in patients with rheumatoid arthritis. This can reflect some well-known etiopathogenetic mechanisms such as the increased prevalence of the shared epitope HLA-DRB1-04, exacerbated T-cell responsiveness with high tissue levels of IL-17, and the presence of *P. gingivalis*, Epstein-Barr virus and cytomegaloviruses (Dissick *et al.* 2010). An increased prevalence of periodontitis in patients with positive rheumatoid factor and positive antibodies against anticyclic citrulline peptide (ACCP) was reported in another study (Pischon *et al.* 2008). A statistically significantly higher prevalence of periodontitis in patients with RA was confirmed in the Pischon *et al.* study, where subjects with RA had significantly increased periodontal attachment loss compared to controls. Oral hygiene played only a minor role in this association (Mirrielees *et al.* 2010). An increase of periodontal inflammation in patients with RA accompanied by higher bleeding on probing (BOP) was detected by means of salivary biomarkers of periodontal disease (Sorensen *et al.* 2008). These studies represent an epidemiological relationship between rheumatoid arthritis and periodontitis, mainly in their immunological features.

REVIEW OF ETIOPATHOGENETIC ASSOCIATIONS BETWEEN RA AND PERIODONTITIS

Direct causal correlations between these two diseases have not yet been precisely established. There are various types of epidemiological, clinical and experimental studies, which mostly confirm some mutual etiological factors and possible positive etiopathogenetic associations between both diseases. Several common risk factors and mutual pathogenetic correlations can be divided into the following groups:

Common genetic associations

a) Participation of common genes

Blood cell genes participating in inflammatory-immune reactions were tested. 14 genes involved in this process were increased in subjects with localized aggressive periodontitis (LAgP), generalized aggressive periodontitis, juvenile idiopathic arthritis (JIPA), and rheumatoid arthritis (RA) compared with the controls. The toll-like receptor 2 gene and the myomesin 2 gene were both increased, which can indicate a possible common genetic etiology of both diseases (Kobayashi *et al.* 2009). Identical subtypes can represent a common immunogenetic basis in the heredity of specific HLA antigens. Variations of subtypes 0401, 0404, 0405 and 0408 on genetic locus HLADR4 are equal and associated with RA prevalence and aggressive periodontitis (Trombone *et al.* 2010; Kobayashi *et al.* 2010).

b) Genetic polymorphisms

In patients with RA, by means of periodontal pockets depth index measurements, attachment loss index and BOP index, the prevalence of periodontitis in 89.5% of the subjects was detected. At the same time 16 gene polymorphisms encoding interleukins /IL/-1, -2, -4, -6, and -10, TNF-alpha, and transforming growth factor beta-1 /TGFbeta-1/ were studied. After division according to age, gender, and smoking status, multiple logistic regression analysis revealed a significant difference in the distribution of IL-1B +3954 genotypes between RA + PD and PD groups and between RA + PD and healthy control groups (Nillson *et al.* 2008). These researches provide important evidence about the possible common genetic basis for both diseases, but further research is essential.

c) Hyper-inflammatory genotype

Nowadays it is obvious that both diseases share the chronic nature of the inflammatory reaction associated with bone resorption activity, whereby the genetically-based hyper-inflammatory genotype is generally associated with increased levels of several pro-inflammatory factors. Associations transmitted in this way were confirmed also in an animal experimental model. Interactions between periodontitis and rheumatoid arthritis shared a hyper-inflammatory genotype and functional interferences in innate and adaptive immune responses (Liao *et al.* 2009).

Participation of inflammatory mediators: Common cytokine profiles

In spite of the fact that an exact causal association between both diseases has not been clearly established,

several studies state that such an association is possible via similar cytokine profiles and associations. In patients with progressive RA, increased serum levels of CRP, IL-6, TNF-alpha, and a statistically important increase of places with positive BOP were both detected (Biyikoglu *et al.* 2009). Some studies report increased levels of TNF-alpha correlating with gingivitis and periodontitis in patients with RA (Bonfil *et al.* 1999). Some common features of both diseases, such as chronic persistent inflammation of crevicular fluid, present a possible pathogenetic model. Sulcular and synovial fluids are filled with pro-inflammatory cytokines that are in fact largely accumulated immune competent cells (Liao *et al.* 2009). These cytokines, mainly IL-1beta, TNF-alpha and IL-17 induce expression of adhesive molecules, and increased production of lipidoid inflammatory mediators and proteolytic enzymes that degrade proteins and stimulate the RANKL osteoclastogenetic factor (Liao *et al.* 2009; Biyikoglu *et al.* 2009).

Cellular and humoral immunity

a) Role of cellular immunity

Cellular immunity elements play a crucial role in the pathogenesis of both diseases. The immune cells are caught from the bloodstream and transported to sites of inflammation region, which can be the synovial membrane or gingival mucosa. There they are transformed into monocytes and other inflammatory and residual cells. These, after stimulation with T-lymphocytes, start production of pro-inflammatory cytokines, including lipoid mediators, oxidative substances, and proteolytic enzymes. The cellular elements and their inflammatory substances have strong antibacterial, oxidative and proteolytic potential, the role of which is to eliminate local infection. A prolonged or altered course of inflammation can destroy local tissue; in our case it is damage to and destruction of gingival tissues and tissues of periodontal ligaments with subsequent destruction of the neighbouring alveolar bone as well as destruction of synovial structures and further damage of adjacent osseous structures and destruction of joint structure and function (Genco 1992; Weissmann 2004).

b) Role of humoral and autoimmune reactions

Studies of associations between periodontitis and rheumatoid arthritis in context with several auto-immune factors and reactions indicate the dominant role of the periodontal pathogen *Porphyromonas gingivalis* /P.g/. *P. gingivalis* was detected in all forms of periodontitis. Its main etiopathogenic activity results in chronic (adult) forms of the disease (Holt 2000).

Several studies have confirmed that the relationship between periodontal infection caused by anaerobic bacteria *P. gingivalis* and rheumatoid arthritis can be mediated by auto-antibodies called anticyclic citrulline peptides /anti-CCP/ among which antivimentin, antiperinuclear factor, antikeratine and antifilagrine antibodies are listed. This group of auto-antibodies is able to distinguish epitopes containing amino acid citrulline, formed by various posttranslational modifications of arginine residues by means of the PAD /Peptidyl Arginine Deiminasa/ enzyme. Deimination, called also citrullination, is an enzymatic reaction causing only a small change of molecular weight but significant changes to the biochemical and antigenic properties of citrulline proteins (Smolik *et al.* 2009; Liao *et al.* 2009).

Some animal studies detected that auto-antibodies against citrullinated proteins are associated with the destructive inflammatory process of rheumatoid arthritis connected with autoimmunization against deimmunized structures of fibrin, the deposits of which in-filter into synovial membranes affected by rheumatitis (Smolik *et al.* 2009; Liao *et al.* 2009; Andersen *et al.* 1972; De Pablo *et al.* 2009).

Citrullination of arginine can also change activation of CD4 T-cells via reactions in the changed epitopes of II class MHC molecules, typical for rheumatoid arthritis. The combination of citrullination and changed epitopes of HLA-DRB can cause altered recognition of genes (Smolik *et al.* 2009; Liao *et al.* 2009; Andersen *et al.* 1972; De Pablo *et al.* 2009, Hill *et al.* 2003).

Nowadays there is evidence that periodontitis could become associated with these auto-immune processes by means of the periodontal pathogen *Porphyromonas gingivalis*.

Microbial factors

a) The role of periodontal pathogens

The relationship between the presence of bacterial pathogens in patients with periodontitis and the presence of clinically confirmed rheumatoid arthritis has been presented in several experimental and clinic-microbiological studies. In the animal model, the fact that pre-existing periodontitis exacerbated development of experimental arthritis was confirmed (Cantley *et al.* 2011).

In patients with periodontitis and RA, during periodontal bacterial DNA identification, a 100% prevalence of these bacteria was detected in subgingival dental plaque and synovial fluid, and 83.5% in serum. In subgingival biofilm and synovial fluid, Prevotella intermedia occurred more often /89.4% and 73.6%. Prevalence of *Porphyromonas gingivalis* in the same structures was 57.8% and 42.1%. We can deduce from these results that periodontal bacteria may have a role in the RA etiology (Martinez-Martinez *et al.* 2009).

b) The role of Porphyromonas gingivalis

As presented above, there is some evidence of correlations between destructive mechanisms in joint structure in patients with RA and the periodontal pathogen *P. gingivalis*. On the basis of this evidence, there is a hypothesis about the possible interconnection of these two diseases. Here though arises the question of how periodontal bacteria can have a pathogenic influence on joint changes in patients with RA. A statistically

important increase in antibodies against *P. gingivalis* is presented both in patients with periodontitis and in patients with RA (Mikuls *et al.* 2009). The question of a possible causal interconnection via *P. gingivalis* is answered with the fact that only these bacteria are able to produce the PAD enzyme, identical to human PAS and responsible for post-translational change of arginine into citrulline. The auto-immune pathogenic potential of this enzyme in development of RA is obvious and was described in the previous paragraph.

Review of hypotheses of associations between periodontitis and RA

a) Non-causal hypotheses

Non-causal hypotheses suggest endogenous (immunological) and environmental factors increase susceptibility to both diseases. These hypotheses are supported by studies dealing with the main risk factors of periodontal etiology that are also risk factors in the etiology of rheumatic arthritis. This group is predominantly made up of various types of genetic polymorphisms. The most frequent genetic polymorphisms introduced here are polymorphisms of pro-inflammatory cytokines, mainly IL-1, polymorphisms of FcR receptors and specific HLA antigens. Identical polymorphisms on locus HLA DR4 were detected for RA and other destructive types of periodontitis (Bonfil *et al.* 1999; De Pablo *et al.* 2009; Bartold *et al.* 2005). The accumulation of additive and anti-reaction genes can have an influence on the inflammatory reaction and can lead to significantly different values of individual components. During evaluation of leukocyte infiltration and concentration of exudative proteins, 2.5 up to 20-fold differences were detected (Vigar *et al.* 2000; Trombone *et al.* 2010). It is necessary to note that several studies support non-causal models of periodontitis and rheumatic arthritis associations. Research results describe interference of several genetic and immunological components and systems as well as the mutual influence of both diseases (Bonfil *et al.* 1999; De Pablo *et al.* 2009; Bartold *et al.* 2005; Vigar *et al.* 2000; Trombone *et al.* 2010).

b) Causal hypotheses

Among causal hypotheses, theories interconnecting both diseases through periodontal pathogens are dominant. Besides hypotheses based on bacteria *P. gingivalis*, there are also results of experiments that investigated the relationship between both diseases by means of infection caused by Aggregatibacter actinomycetemcomitans /A.a/. However exact causal and molecular correlations were not precisely established. Some studies take into consideration a cross-reaction of oral bacteria epitopes via RF (Trombone *et al.* 2010; Yoshida *et al.* 2001; The *et al.* 1996).

The influence of periodontal and rheumatoid therapy on the course of both diseases

Some clinical studies have confirmed a positive impact of non-surgical periodontal therapy on the activity and course of rheumatologic disease; similarly rheumatologic therapy has had a positive influence on several periodontal parameters. Dental hygiene in patients with periodontitis and RA significantly improved some score of RA activity and the sedimentation rate of erythrocytes. Equally anti TNF-alpha therapy significantly decreased the values of several periodontal indices (Ortiz *et al.* 2009).

CONCLUSION

1. The incidence of RA in patients with periodontitis is about 3.95 versus the incidence of RA in the general population, which varies from 0.5 to 1.0%. In arthritic patients, some inflammatory periodontal parameters were significantly increased. These epidemiological correlations work both ways: in patients with periodontitis the prevalence of rheumatoid arthritis was increased two-fold.
2. Periodontitis and rheumatoid arthritis have severe histo-pathological and tissue-inflammatory correlations. They present a chronic inflammatory process of soft and connective tissues in the form of destructive inflammation of gingiva, tissues of periodontal ligaments, synovitis and destructive inflammation of joint cartilages. Tissue washed with inflammatory synovial and crevicular fluid; in direct contact with bone tissue (tooth root, joint bone) and different inflammatory osteolytic destruction degrade the bones.
3. In both diseases common etiological risk factors have been both supposed and determined. Nowadays, although the exact causal association between the diseases has not been fully established, there are several common groups of etiopathogenetic correlations and risk factors. When considering a possible genetic association, we should look at common genes, genetic polymorphisms of immunologically active molecules and immunity competent cells mutually influencing an inflammatory reaction as well as hyper-inflammatory genotype of some components of protective inflammatory reaction.
4. In the etiology of both diseases, a certain role is played by common cytokine profiles. In patients with RA, increased levels of these profiles in periodontal tissues and in crevicular fluid have been detected; in patients with periodontitis, increased concentrations of cytokines in joint structures, including synovial fluid, were detected.
5. The pathogenesis of both diseases is similar, with participation of various elements of cellular and humoral immunity. Excessive or altered anti-inflammatory reactions in the periodontium and joint structures reflect some common factors and mecha-

nisms, the result of which is the inflammation-induced self-destruction of connective and osseous structures.

6. The effect of an autoimmune reaction was proved in RA. This is proved also by the existence of the rheumatoid factor (RF) and anticitrulline antibodies (anti-CCP). Anti-cyclic citrulline peptides are auto-antibodies against citrulline amino acid, which is manufactured from arginine by means of PAD enzyme and is called deimination. These auto-antibodies react against deiminated fibrin structures, whose deposits infilter into joint synovium afflicted with rheumatism.
7. Microbial factors, in the form of periodontal pathogens, are the major etiological factors in periodontitis. Nowadays there is a hypothesis that one of them, *Porphyromonas gingivalis*, produces a PAD enzyme similar to humoral PAD. If bacterial PAD could citrullinate arginine, the connection between the diseases would assume a causal character. However further research of this issue is needed first.
8. The results of several studies refer to the beneficial effects of conventional periodontal therapy on some parameters of rheumatoid arthritis. Analogically some of the latest therapeutic procedures used in RA therapy, such as anti-cytokine treatment, provide a good basis for collaboration between periodontologists and rheumatologists in the treatment of both diseases.

REFERENCES

1 Andersen RB, Elling P (1972). Immunofluorescent demonstration of intracellular fibrin in synovial tissue. Ann. Rheum. Dis. **31**: 59–64.
2 Bartold PM, Marschall RI, Hayness DR (2005). Periodontitis and rheumatoid arthritis: a review. J. Periodontol. **76**: /11 Suppl/, 2066–2077.
3 Berthelot JM, Le Goff B (2010). Rheumatoid arthritis and periodontal disease. In: Joint, Bone, Spine: Revue de Rheumatisme. **77**: 537–41.
4 Biyikoglu B, Buduneli N, Kardesler L, Aksu K, Pitkala M, Sorsa T (2009). Gingival crevicular fluid MMP-8 and -13 and TIMP-1 levels in patients with rheumatoid arthritis and inflammatory periodontal disease. J. Periodontol. **80**: 1307–1314.
5 Bonfil JJ, Dillier FL, Mercier P, Reviron D, Foti B, Sambuc R, *et al.* (1999). A case control study of the role HLADR4 in severe periodontitis and rapidly progressive periodontitis. J. Clin. Periodontol. **26**: 77–84.
6 Cantley MD, Haynes DR, Marino V, Bartold PM (2011). Pre-existing parodontitis exacerbates experimental arthritis in mouse model. J. Clin. Periodontol. **38**: 532–541.
7 De Pablo P, Chapple IL, Buckley CD, Dietrich T (2009). Periodontitis in systemic rheumatic disease. Nature Reviews Rheumatology. **5**: 218–224.
8 Dissick A, Redman RS, Jones M, Rangan BV, Reimold A, Griffiths GR *et al.* (2010). Association of periodontitis with rheumatoid arthritis. J. Periodontol. **81**: 223–230.
9 Genco RJ (1992). Host response in periodontal diseases: Current concepts. J. Periodontol. **63**: 338–355.
10 Hill JA, Southwood S, Sette A, Jevnikar AM, Bell DA, Cairns E (2003). The conversion of arginin to citrullin allows for a high-affinity peptide interaction with the reumatoid arthritis associated HLA-DRB1 0401 MHC class II molecule. Journal of Immunology. **171**: 538–541.
11 Holt SC, Kesavalu L, Walker S, Genco R (1999). Virulence factors of *Porphyromonas gingivalis* in Slots J.: Actinobacillus actinomycetemcomitans and Porpyromonas gingivalis in periodontal disease. Periodontology 2000. **20**: 168–238.
12 Kobayashi T, Murasawa A, Ito S, Yamamoto K, Komatsu Y, Abe A, *et al.* (2009). Cytokine gene polymorphism associated with reumatoid arthritis and periodontitis in Japanese adults. J. Periodontol. **80**: 792–799.
13 Kobayashi T, Yokoyama T, Ishida K, Abe A, Yamamoto K, Yoshie H (2010). Serum cytokine and periodontal profiles in relation to disease activity of rheumatoid arthritis in Japanese adults. J. Periodontol. **81**: 650–657.
14 Liao F, Li Z, Wang Y, Shi B, Gong Z, Chenq X (2009). *Porphyromonas gingivalis* may play an importent role in pathogenesis of periodontitis-associated rheumatoid arthritis. Medical Hypotheses.**72**: 732–735.
15 Loeshe WJ (1994). Periodontal disease as a risk factor for heart disease. Compendium. **15**: 976, 978–982, 985–986.
16 Martinez-Martinez RE, Abud-Mendoza C, Pationo-Marin N, Rizo-Rodriguez JC, Little JW, Loyola-Rodriguez JP (2009). Detection of periodontal bacterial DNA in serum and synovial fluid in refractory rheumatoid arthritis patients. J. Clin. Periodontol. **36**: 1004–1010.
17 Mikuls TR, Payne JB, Reinhardt RA, Thiele GM, Maziarz E, Cannella AC, *et al.* (2009). Antibody responses to *Porphyromonas gingivalis* /P. gingivalis/ in subjects with rheumatoid arthritis. Internationational Immunopharmacology. **9**: 38–42.
18 Mirrielees J, Crofford LJ, Lin Y, Kryscio RJ, Dawson DR, Ebersole JL *et al.* (2010). Rheumatoid arthritis and salivary biomarkers of periodontal disease. J. Clin. Periodontol. 37: 1068–1074.
19 Nillson M, Kopp S. (2008). Gingivitis and periodontitis are related to repeated high levels of circulating tumor necrosis factor-alpha in patients with rheumatoid arthritis. J. Periodontol. **79**: 1689–1696.
20 Ortiz P, Bissada OP, Palomo L, Han YW, Al-Zahrani MS, Paneerselvam A, *et al.* (2009). Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factors inhibitors. J. Periodontol. **80**: 535–40.
21 Pischon N, Pischon T, Krőger J, Gülmez E, Kleber BM, Bernimoulin JP, *et al.* (2008). Association among rheumatoid arthritis, oral hygiene, and periodontitis. J. Periodontol. **79**: 979–986.
22 Smolik I, Robinson D, El-Gabalawy (2009). Periodontitis and rheumatoid arthritis: epidemiologic, clinical, and immunologic associations. Compendium of Continuing education in dentistry. **30**: 188–190, 192, 194 passim; quiz 198, 210.
23 Sorensen LK, Havemose-Poulsen A, Sonder SU, Bendtzen K, Holmstrup P (2008). Blood cell gene expression profilling in in subjects with aggressive periodontitis and chronic arthritis. J. Periodontol. **79**: 477–485.
24 The J, Ebersole JL (1996). Rheumatoid factor from periodontitis patients cross-react with epitopes on oral bacteria. Oral Diseases. **2**: 253–262.
25 Trombone AP, Claudino M, Colavite P, de Assis GF, Avila-Campos MJ, Silva JS, *et al.* (2010). Periodontitis and arthritis interaction in mice involves a shared hyper-inflammatory genotype and functional immunologicalinterferences. Genes Immun. **11**: 479–489.
26 Vigar ND, Cabrera WA, Araujo LM, Ribeiro OG, Ogata TR, Siqueira M, *et al.* (2000). Pristane induced arthriris in mice selected for maximal or minimal acute inflammatory reaction. Eur. J. Immunol. **30**: 431–437.
27 Weissmann G (2004). Pathogenesis of reumatoid arthritis. Journal of Clinical Rheumatology. **10**: 526–531.
28 Yoshida A, Nakano Y, Yamashita Y, Oho T, Ito H, Kondo M, *et al.* (2001). Immunodominant region of Actinobacillus actinomycetemcomitans 40-kilodalton heat shock protein in patients with reumatoid arhritis. J. Dent. Res. **80**: 346–350.