

Rheumatoid Arthritis and Periodontitis-Plausible Inflammatory Link

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DOI: <http://dx.doi.org/10.13005/bpj/763>

(Received: August 15, 2015; accepted: September 20, 2015)

ABSTRACT

An association between oral disease/periodontitis and rheumatoid arthritis (RA) has been considered for more than a century. RA is considered as an autoimmune disease whereas periodontitis has an infectious etiology with a complex inflammatory response. In spite of the controversial etiology, both diseases are chronic and may present with bursts of disease activity. Genetic factors are driving the host responses in both RA and periodontitis. The inflammatory events are regulated by Tumor necrosis factor - α , a proinflammatory cytokine, in both RA and periodontitis. *Porphyromonas gingivalis* is a common pathogen in periodontal infection. *P. gingivalis* has also been identified in synovial fluid. The specific abilities of *P. gingivalis* to citrullinate host peptides by proteolytic cleavage at Arg-X peptide bonds by arginine gingipains can induce autoimmune responses in RA through development of anticyclic citrullinated peptide antibodies. In addition, *P. gingivalis* carries heat shock proteins (HSPs) that may also trigger autoimmune responses in subjects with RA. Data suggest that periodontal therapies combined with routine RA treatments further improve RA status. This review enlightens the link between periodontitis and rheumatoid arthritis.

Keywords: rheumatoid arthritis, periodontitis, bacteria, inflammation, *Porphyromonas gingivalis*, citrullination, genetics.

INTRODUCTION

There is growing awareness of the link between periodontal and systemic inflammatory conditions such as (RA) and coronary artery disease based on common etiopathogenic mechanisms. RA, is characterized by chronic synovitis with the resultant damage to joint cartilage and bone which in turn is accompanied by joint pain and reduced mobility affecting 1% of the adult population.¹ Chronic periodontitis, initiated by bacterial plaque² is prevalent in a third of the population beyond the age of 50 years and 10%–15% of all adults,³ being the main cause of tooth loss in adults. Chronic infection and persistent

inflammation are likely to play an important role in the pathogenic progression of atherosclerosis and coronary artery disease.⁴ There is documented evidence of the link between periodontal disease, acute myocardial infarction;^{5,6} and between periodontitis and arthritis.⁷⁻⁹

Oxidative stress induced by cytokines in periodontitis, and RA

Periodontal disease has a multifactorial etiopathogenesis, affecting a large proportion of the adult population. Increased levels of C-reactive protein (CRP) and other markers of inflammation are identified. Raised levels of CRP reflect an increased risk of cardiovascular disease. Certain

pathological features of atherogenesis are seen in RA, associated with macrophage-activating cytokines tumor necrosis factor- α (TNF- α), the interleukins IL-1, IL-6, raised levels of the inflammatory marker (CRP) and the enhanced expression of endothelial adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1);¹⁰ which is also relevant to chronic periodontitis.

The role of periodontal pathogens in chronic periodontitis, RA

Porphyromonas gingivalis (*Pg*) is a significant periodontal pathogen; it is the only bacterium known to possess a peptidyl arginine deiminase (PAD) which generates a citrullinated peptide by post-translational modification (citrullination) of protein bound arginine; the citrullinated peptide and anti-cyclic citrullinated peptide (anti-CCP) autoantibody are capable of breaking down self-tolerance and lead to the development of autoimmune RA.¹¹

Constant production of PAD by *Pg* could result in citrullination of fibrin in the synovium; antigens presented in association with MHC molecules by antigen presenting cells leads to the production of anti-CCP antibody. These antibodies form immune complexes with citrullinated proteins, which can bind to inflammatory cells via their Fc receptors, leading to activation of the complement cascade. The resultant release of inflammatory mediators leads to joint destruction and RA. Uncontrolled periodontal disease could play a role in the development of RA via peptide citrullination involved in loss of self-tolerance and autoimmune destruction of synovial tissue.

Periodontitis, rheumatoid arthritis, and genetic factors

In 1987, a successful demonstration of the connection between HLA-DR4 and rapidly progressive periodontitis (RPP) by specific typing

of the HLA gene loci HLA-A, HLA-B, HLA-C, and HLA-D was achieved. In that study, a DR4 frequency of 80% in patients with RPP as opposed to 38% in the control group was observed.¹²

Heat shock proteins and RA

Heat-resistant, hydrophilic molecules with a molecular weight of 24 to 30 kDa are referred to as superantigens. They are able to virtually glue together T-cell receptors (TCRs) and major histocompatibility complex II molecules,¹³ which trigger a permanent signal in T cells. These superantigens of RA can be influenced by oral bacteria, such as *P. gingivalis* and *P. intermedia*.

A greater prevalence of periodontal disease and tooth loss has been reported amongst subjects with RA. Autoimmune inflammatory responses that occur in RA may be sustained as a result of periodontal inflammation, which could represent a risk factor for RA, altered by treatment.¹⁴ Common genetic and environmental factors could predispose to both independently. Both RA and periodontal disease have a wide prevalence amongst inflammatory diseases with several common mechanisms in their pathogenesis associated with tissue destruction.

CONCLUSION

Periodontal infection (*P. gingivalis*) carries a unique risk for development of autoimmune antibodies associated with RA. Patients with RA have either lost many teeth or usually have severe periodontitis. Additional research, both in regards to basic mechanisms as well as clinical studies, are necessary before it can be said that there are causative links between RA and periodontitis. Cross-disciplinary research in well-defined populations should be performed to further enhance knowledge and develop clinical strategies how to coordinate therapy and risk assessments of RA and periodontitis.

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