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Published in:
Anaerobe

DOI:
10.1016/j.anaerobe.2011.03.019

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2011

Anaerobe 17 (2011) 196–200

Contents lists available at ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe

Clinical Microbiology

Rheumatoid arthritis and periodontitis; a possible link via citrullination

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ARTICLE INFO

Article history:
Received 1 November 2010
Received in revised form
2 March 2011
Accepted 29 March 2011
Available online 16 April 2011

Keywords:
Rheumatoid arthritis
Periodontitis
Porphyromonas gingivalis

ABSTRACT

Rheumatoid Arthritis (RA) and chronic and aggressive periodontitis are chronic inflammatory disorders characterized by deregulation of the host inflammatory response. Increased secretion of pro-inflammatory mediators results in soft and hard tissue destruction of the synovium and periodontium respectively. Both diseases share risk factors and have pathological pathways in common, resulting in loss of function and disability as a final clinical outcome. This article discusses possible interactions, particularly related to the periodontal pathogen *Porphyromonas gingivalis*, which could explain the observed association between these two prevalent diseases.

1. Periodontal disease

Supragingival plaque accumulation results in an inflammatory response of the gums and is called gingivitis. This infection can be eliminated by reduction of the total bacterial load through simple oral hygiene measures. When the infection proceeds, destructive periodontal disease or periodontitis can develop in susceptible individuals. Periodontitis is an infective process with destruction of the supporting soft and hard tissue of the teeth (the periodontium) as a consequence. It can be can be characterized as chronic (slowly progressive) or aggressive (highly destructive) forms of periodontitis. Further classification can be made on the extent (localized/generalized) and severity (mild/moderate/severe) of the disease [1]. Clinical signs of the disease are bleeding gums, deepened periodontal pockets, suppuration and in an advanced stage, mobility of the teeth with tooth loss as the final disease outcome due to extensive loss of alveolar bone. Periodontitis is a multifactorial, bacterial driven, chronic inflammatory disorder that occurs in 10–15% of an adult population, independent of ethnicity and geographic location [2]. It is the major factor for tooth loss over the age of 35 years. Bacteria play a major role in etiology; it is thought that the biofilm in the subgingival area causes a chronic inflammatory response that is responsible for destruction of the alveolar bone and soft tissue surrounding the teeth (the periodontium). The subgingival biofilm in periodontal lesions consists of hundreds of bacterial species, most of which are strict anaerobic and of which a significant part is non-cultivable. Cultivable microbial indicators for periodontitis are, among others, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Parvimonas micra*, *Treponema* species and *Tannerella forsythia* [3].

Although bacteria are essential for periodontal disease to occur, a susceptible host is also required. It is thought that susceptibility is determined by genetic traits and lifestyle factors such as smoking and stress. Identified risk factors for the initiation of periodontitis are subgingival calculus and subgingival detection of *A. actinomycetemcomitans* [4]. Risk indicators for progression of the disease include smoking [5], age, stress and psychological factors [6] and existing attachment loss [7]. Other putative risk factors involve gender, education, socio-economic status [8], nutritional factors [9] and body mass index [6,10].

2. Periodontitis is not a local phenomenon

In generalized severe chronic and aggressive periodontitis the infected and necrotic epithelium surface area amounts up to 20 cm^2. Periodontal lesions may lead to bacteremia that can be the cause of focal infection of dental origin [11–13]. Severe periodontitis also results in a continuous systemic inflammatory response [14–16]. Periodontitis has been associated with a number

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doi:10.1016/j.anaerobe.2011.03.019

of other chronic and inflammatory diseases such as diabetes mellitus [17], atherosclerosis, cardiovascular disease and stroke [18], rheumatoid arthritis [19,20], Crohn's disease and ulcerative colitis [21] and preterm birth and low birth weight [22]. In this paper we review current knowledge on the association of periodontitis and rheumatoid arthritis and discuss possible mechanisms of interactions between the two disorders.

3. Rheumatoid arthritis and anti-citrullinated protein antibodies

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis with a prevalence of 0.5%–1.0% of adults in industrialized countries. The disease is far more common among women than men (3:1) and prevalence rises with age, with a peak in the fifth decade [23]. The etiology is multifactorial and the pathogenesis is poorly understood. Autoimmunity to citrullinated proteins is highly specific for RA and may be of pathogenic significance [24]. Risk of developing RA is of 50% attributable to genetic factors [25]. Smoking is the major known environmental risk factor for RA. Smoking and genetic risk factors interact in providing an increased risk of RA [26]. Immune responses with several inflammatory cascades lead toward a final common pathway with persistent synovial inflammation and associated damage to articular cartilage and underlying bone as a consequence. There is evidence of a preclinical or asymptomatic phase of the disease, in which autoantibodies can be already be present [27]. The auto-antibodies most frequently found in patients with RA are antibodies which bind to the constant domain of IgG molecules (IgM rheumatoid factor, IgM-RF) and antibodies against citrullinated proteins (anti-citrullinated protein antibodies, ACPA). The majority of individuals with RA (50–80%) have serum positive titers for IgM-RF and/or ACPA. ACPA have a higher specificity (98%) and sensitivity (up to 80%) for diagnosis of RA than IgM-RF [28]. ACPA seem to be better predictors of poor prognosis of RA; ACPA-positive RA is associated with increased joint damage and low remission rates [29]. ACPA exist in around 2% of normal populations and are rare in other inflammatory conditions [30]. ACPA were originally measured as antibodies against keratin (the anti-perinuclear factor) [31], and more recently as anti-cyclic citrullinated peptides (anti-CCP) [32]. These autoantibodies recognize epitopes containing citrulline. Citrulline is a nonstandard amino acid, and is therefore not incorporated in proteins during translation. However, it can be generated by post-translational modification (citrullination) of protein-bound arginine by peptidylarginine deiminase (PAD) enzymes. This post-translational modification may have a big impact on the structure and function of the target protein, partly due to a change of charge. Citrullination is an inflammation-associated phenomenon, occurring in a wide range of tissues. It is predominantly observed in proteins of the cytoskeleton. It seems to represent a general regulatory mechanism, particularly occurring during apoptosis. So far, five isotypes of PAD have been described in humans. All these enzymes rely strongly on the presence of calcium for activity and are unable to convert free L-arginine into L-citrulline, which can be done by nitric oxide synthase in eukaryotes or by arginine deiminase in bacteria. Because of their calcium dependency, PAD enzymes are more likely to be active in the extracellular compartment. PAD2 and PAD4 are found in synovial fluid and in synovial tissue of RA patients and are therefore the most likely candidate PAD isotypes for the citrullination of synovial proteins in RA [33]. Smoking enhances PAD2 expression in human lungs with consequent generation of citrullinated proteins in the bronchoalveolar compartment [34]. Recently, PAD2 expression and citrullinated proteins have also been detected in the periodontium [35]. Whereas citrullination is associated with inflammation in general, the development of antibodies against them (ACPA) is specific to RA. The high specificity of ACPA is therefore most likely the result of an abnormal humoral response to these proteins. ACPA are produced locally in the inflamed synovium [36], suggesting that the resulting immune complexes are directly involved in the disease pathogenesis of the chronic inflammation in the rheumatoid joint. If there is local ACPA production in the periodontium or in the bronchoalveolar compartment remains to be established, albeit higher ACPA reactivity in serum samples of aggressive periodontitis patients has been reported [37].

3.1. Similarities between RA and periodontitis

There are remarkable similarities between RA and chronic and/or aggressive periodontitis. Both diseases are chronic destructive inflammatory disorders characterized by deregulation of the host inflammatory response. The etiology of both diseases is multifactorial and susceptibility to the diseases is influenced by shared genetic and lifestyle factors. Both diseases are cumulative, i.e. severity, loss of function and quality of life decrease with longer disease duration. There are common pathological mechanisms; both conditions are potentiated by an exaggerated inflammatory response featuring an increase in localized and perhaps circulating pro-inflammatory mediators, resulting in soft and hard tissue destruction of the periodontium and synovium respectively.

A number of clinical studies point toward an association between periodontal disease and RA [38], despite the fact that patients suffering from RA are often treated with immune suppressant corticosteroids, thereby possibly reducing clinical evidence of periodontal disease. An important observation is that treatment of periodontal disease has a positive effect on disease activity of RA [39], although this observation needs further confirmation. Surprisingly, none of the studies on RA and periodontal disease considered microbiology, although bacteria play a primary role in the etiology of periodontal disease. Similarities in risk factors, common pathological pathways, association in prevalence and the effect of periodontal treatment on RA make us look further to explore the relation between periodontitis and RA, with a special focus on microbiology.

4. The Bradford Hill approach

To describe the strength and nature of an association between two disorders, the widely used Bradford Hill criteria to determine a causal association are applied [40]. These involve strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy of the association. Starting from epidemiologic evidence, four issues need to be addressed: strength, consistency, temporal relation, and analogy. The third National Health and Nutrition Examination Survey (NHANES III) is a nationally representative cross-sectional survey of non-institutionalized US population. Using this data, de Pablo et al. [41] included participants aged $\geq$60 years who had undergone both musculoskeletal and dental examinations ($n = 4461$). They found that subjects classified with RA, according to the American College of Rheumatology (ACR) criteria of 1987 ($n = 103$), were more likely to suffer from periodontitis, after adjusting for age, sex, ethnicity and smoking. Considering three out of six ACR criteria, they found an odds ratio (OR) of 1.8, considering four out of six ACR criteria an OR of 4.1. Participants with RA had significant more missing teeth than participants without RA. Comparing periodontal status in 65 RA patients (according to the ACR criteria 1987) with an age- and gender-matched control group (age range 20–70 years) without RA, Mercado et al. [42] found that individuals with RA are more likely to experience more periodontal

disease (OR 2.2) compared to individuals without RA. Individuals in the RA group showed significant more missing teeth compared to the non-RA group, an observation that confirms previous findings [43,44]. Indicators of disease activity for RA most positively correlated with periodontal bone loss were the number of swollen joints, health assessment questionnaire scores, levels of C-reactive protein and erythrocyte sedimentation rates. The other way around, in 1412 individuals attending the University of Queensland's School of Dentistry, Mercado et al. [45] found that self-reported RA was significantly higher in patients referred for periodontal treatment ($n = 809$) compared to patients not referred for periodontal treatment (3.95% vs. 0.66%). Nesse et al. [20] found in a cross-sectional study an increased prevalence of RA in patients with periodontitis, which could not be explained by the confounding factors sex, age and smoking. Coherence of the association is influenced by variation in design, setting, methods, selection bias and the fact that the majority of the studies on this association are low-prevalence case-control studies with no consistent criteria to define periodontitis. With respect to temporal relation, specific auto-antibodies (IgM-RF and ACPA) precede the symptoms of RA [27]. Half of patients with RA have specific serologic abnormalities several years (median 4.5 years) before the development of clinical symptoms. Besides the analogy of the characteristics of the population to which the diseases are exposed, the two diseases have pathological mechanisms in common and they share environmental and genetic risk factors. If there is a dose–response relation between the two diseases is currently unknown. The available studies on association of periodontitis and RA did not quantify the extent of periodontal disease, but is now possible with the Periodontal Inflamed Surface Area (PISA) index for inflammatory burden [46]. Nevertheless, antibody titers to the periodontal pathogen *P. gingivalis* are increased in patients with RA and there are significant positive correlations between *P. gingivalis* antibody titers, CRP concentrations and antibody titers to citrullinated proteins, i.e. to disease specific immunity [47]. Biological plausibility is partly explained by this association, and the fact that periodontitis causes an inflammatory burden by eliciting a systemic inflammatory response. Antibody response to *P. gingivalis* and DNA of *P. gingivalis* self have been found in synovial fluid of RA patients [48–50]. Experimental evidence is drawn from two controlled studies that have been conducted on the effect of periodontal treatment on RA [39,51]. Both studies showed that periodontal therapy had a beneficial effect on laboratory RA parameters and clinical symptoms of RA. Because these studies had a small sample size and did not consider microbiology, there is a crying need for better designed experimental studies on the effect of periodontal treatment on RA disease activity.

5. Genetic factors in RA and periodontal disease

In both diseases, candidate gene approach revealed mainly genetic variations in genes encoding for elements of the innate immune system as a risk indicator. More than 30 genetic regions are associated with RA. Genetic variations in the major histocompatibility complex, class II, DR beta 1 (HLA-DRB1) and protein tyrosine phosphatase (PTPN22) genes are the major genetic risk indicators that have been reproducibly identified so far. The association of a number of specific HLA-DRB1 alleles is seen exclusively for the ACPA-positive subset of RA [52]. These HLA alleles share a common peptide-binding motif known as the shared epitope (SE). Antigen modification by protein citrullination is thought to allow antigens to fit in the HLA alleles that hold this SE. The result is breaking of tolerance and antibody formation against these antigens [53]. The PTPN22 gene codes for a tyrosine phosphatase, with a potential function in the regulation of T-cell and B-cell activation. The best-studied environmental factor in RA is smoking and this seems to be a risk factor for ACPA-positive disease, especially in the context of positivity for HLA-DRB1 SE alleles [54]. Studies have also shown an additive interaction between PTPN22 and smoking. No gene–gene interaction was observed between PTPN22 and HLA-DRB1 SE [55].

Genetic and lifestyle factors (smoking) have become the leading susceptibility factors in periodontal disease. The family background and the familial aggregation of early onset aggressive periodontitis have long been recognized. This supports the connection between certain genes' mutation and periodontal disease manifestation. Like RA, among candidate genes possibly associated with increased host immune susceptibility to periodontitis are HLA-DR polymorphisms. A significant association was found between HLA-DRB1 SE and severe periodontitis (chronic/aggressive), stratified according to ethnogeographic origin [56]. Several single nucleotide polymorphisms, notably in the IL1, IL6, IL10, vitamin D receptor, and CD14 genes have been linked to severity and presence of destructive periodontal disease [57]. Genes that encode for IL-1 production have received attention as potential predictors of periodontal disease progression, because of its involvement in the regulation of the host's inflammatory response and bone resorption. IL-1 is not only involved in signaling processes resulting in autoimmune induced bone destruction but also in several hereditary auto-inflammatory syndromes. Meta-analysis of four common promoter SNPs in the IL1 region in British Caucasian patients revealed an association with increased susceptibility to RA [58]. Irrespective of smoking and presence of *P. gingivalis* and *A. actinomycetemcomitans*, patients with severe periodontitis (chronic and/or aggressive) showed a significantly higher frequency of the positive IL1 genotype than periodontally healthy individuals (42% vs. 11%, all Caucasian subjects) [59]. In a study of 42 patients (1044 teeth) in maintenance care for 14 years, the combined effect of a positive IL1 genotype and smoking did increase the risk of tooth loss by 7.7 times, compared to 2.7 and 2.9 times for positive IL1 genotype and smoking separately [60]. Also, gene polymorphisms in pro-inflammatory cytokines IL6 and the IL1 cluster are associated with systemic inflammation in patients with severe periodontitis (chronic and/or aggressive, 65% European Caucasians) [15].

5.1. A link via citrullination

Given the fact that antibody formation against citrullinated proteins plays a major role in autoimmunity in RA, and given the fact that citrullination seems to be a unique feature for the periodontal pathogen *P. gingivalis*, we hypothesize that the onset and progression of RA is influenced by the presence of periodontal infection with *P. gingivalis*.

The bacteria involved in periodontitis accumulate in a subgingival biofilm that comprises predominantly Gram negative strict anaerobic rods. The group of dark-pigmented anaerobic rods is strongly associated with destructive periodontal disease and the major pathogen in this group is *P. gingivalis* [61]. The prevalence of *P. gingivalis* in severe periodontitis is 70% and it has been infrequently isolated from subjects without periodontitis [3], suggesting that this bacterium is not a normal inhabitant of a healthy periodontium [62]. To date, the single prokaryotic enzyme that can citrullinate proteins, has been identified in *P. gingivalis* [63]. Based on the biochemical characteristics and properties of this PAD enzyme, it could be a virulence agent. *P. gingivalis* PAD deiminates the guanidino group of carboxyl-terminal arginine residues on a variety of peptides, to yield ammonia and a citrulline residue. In contrast to human PAD, it can convert both peptidylarginine and free L-arginine and is not dependent on calcium [64].

Known antibodies to citrullinated proteins, the specific serological markers for RA, include anti-citrullinated keratin (the anti-perinuclear factor), anti-citrullinated vimentin (formerly known as the Sa-antigen), anti-citrullinated filaggrin, anti-citrullinated fibrin(ogen) and anti-citrullinated α-enolase antibodies. Alpha-enolase is a multifunctional protein, best known for its role in glucose metabolism and more recently as a plasminogen-binding protein on the surface of various mammalian and prokaryotic cells [65,66]. In RA, the immunodominant epitope of human α-enolase is citrullinated-enolase-peptide-1 (CEP-1). This epitope (amino acids 5–21) shows 82% sequence similarity with CEP-1 of *P. gingivalis*. The amino acids 13–21 are 100% identical. Antibodies purified for affinity to human CEP-1 cross-reacted with CEP-1 of *P. gingivalis* [67].

Recently, Wegner et al. [68] showed that PAD from *P. gingivalis* is able to citrullinate its endogenous proteins and more strikingly, also human fibrinogen and human α-enolase. This seems to be a unique characteristic of *P. gingivalis* [58]. Thus, the immune system in patients with periodontal infection with *P. gingivalis* is exposed to citrullinated antigens that might become systemic immunogens; directly, or via molecular mimicry and cross-reactivity. Peridontal infection with *P. gingivalis* could contribute to the total antigenic load of citrullinated proteins, generated by host PAD during the inflammatory response and by bacterial PAD produced as a virulence factor of *P. gingivalis*. In a genetic susceptible host, for example in context of HLA-DRB1 SE, this could result in a pathologic immune response, with the formation of ACPA and joint inflammation as a consequence. Our hypothesis is that periodontitis and RA are related through common genetic and lifestyle risk factors, inflammatory burden, and in particular in presence of *P. gingivalis* (Fig. 1). To come back to the Bradford Hill criteria, biological plausibility is partly explained by the fact that periodontitis causes a systemic inflammatory response. The association of *P. gingivalis* with the RA-related anti-citrullinated protein antibody response could be a second explanation of this association. Sequence similarity and cross-reactivity with immunodominant epitopes of citrullinated proteins and their bacterial variants may indicate a role for *P. gingivalis* in autoimmunity in patients with RA. To fulfill the Bradford Hill criteria in detail, studies linking periodontal disease and RA need further investigation. If there is a distinct relation, treatment of periodontitis is thought to be of influence on disease activity of RA. By studying (pre)clinical and (micro)biological markers of both diseases, we intend to further unravel the pathogenic relation between periodontitis and RA. Recognition of the association between RA and periodontitis on both a clinical and biologic level may result in new opportunities for intervention that will modify the course of these prevalent debilitating chronic inflammatory disorders.

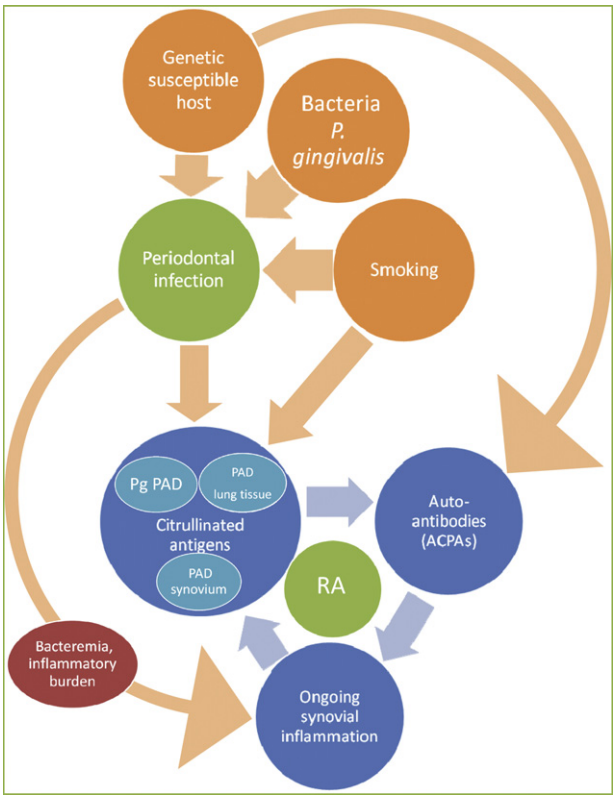

Fig. 1. Possible interactions of periodontal infection with *P. gingivalis* in etiology and pathogenesis of ACPA-positive RA. RA and periodontal infection share genetic traits, lifestyle risk factors as smoking and gene–environmental interactions (for details see text). Infection with *P. gingivalis* can cause bacteremia and generates a systemic inflammatory response, thereby contributing to the total inflammatory burden. In addition, *P. gingivalis* is able to citrullinate proteins. Given the fact that citrullination is an inflammation-associated process, *P. gingivalis* contributes in two ways to the total antigenic load of citrullinated proteins. Smoking contributes to citrullination as well. A susceptible host forms antibodies against the citrullinated proteins (ACPA), which are highly specific for RA. Immune-complex formation sustains synovial inflammation, representative for the laboratory parameters and clinical symptoms of RA.

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