Chapter 6

Rheumatoid Arthritis and Periodontal Disease: A Complex Interplay

Codrina Ancuta, Cristina Iordache,
Eugen Ancuta and Claudia Mihailov

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/65863

Abstract

Recent advances in understanding the dynamic pathways involved in the pathogenesis of rheumatoid arthritis have emphasized the pivotal role of pro-inflammatory cytokines, inflammatory cells, endothelial cell activation and matrix degradation, acting in a genetically predisposed environment. On the other hand, there are significant amounts of data highlighting the potential role of bacteria (leading periodonthopatic pathogen *Porfiromonas gingivalis*) in promoting different types of arthritis, as well as the influence of periodontis (an infectious-inflammatory condition) as etiological or modulating factor in different pathologies, including cardio-vascular disorders, diabetes, respiratory disease and inflammatory rheumatic disorders (such as rheumatoid arthritis, ankylosing spondylitis and lupus). The present chapter deals with the possible association between rheumatoid arthritis and periodontitis as entities with common pathological events.

Keywords: rheumatoid arthritis, periodontitis, *Porfiromonas gingivalis*, citrullination, anti-citrullinated antibodies

1. Introduction

Rheumatoid arthritis (RA) and periodontitis are chronic inflammatory disorders that share a complex, multifaceted host-mediated pathobiology promoted by significant levels of inflammatory mediators that are able to induce synovium and periodontal tissues inflammation, joint damage and alveolar bone loss, respectively [1–7].

RA, a chronic inflammatory autoimmune disease with articular as well as systemic consequences, is outlined by a dynamic pathobiology with chronic synovitis as the epicenter of immunologic responses, inflammation and tissue destruction, occurring as a response to an initiating event (microbial exposure) or a putative antigen in genetically predisposed host [1–11].

On the other hand, known as a destructive, dysbiotic inflammatory condition that concerns gums, periodontal disease or periodontitis is typically characterized by rapid tooth loss directed by local anaerobic bacterial colonization (the "red complex" microorganisms with leading *Porphiromonas gingivalis*), biofilm-related periodontal inflammation, subsequent neutrophilic and immune activation, soft tissue destruction and alveolar bone loss [1–12].

The bidirectional relationship between periodontitis and RA is governed by common genetic (HLA-DR) and environmental influences (smoking), chronic inflammatory events with immunoregulatory imbalance (excessive TNF-α, IL-1β, IL-6, IL-11, IL-17 activation, prostaglandin E2, nitric oxide, matrix metalloproteinases), osteoclast activation (RANKL overregulation) promoting active bone destruction and periodontal lesions, bacterial factors, persistence of antigens, citrullination of endogenous proteins by the means of peptidyl arginine deiminase as second inflammatory event [1–13].

Furthermore, the association among periodontal disease and RA has been extensively addressed in recent years, emphasizing the role of gingival microorganisms, particularly *Porphyromonas gingivalis* (*P. gingivalis*), as the underlying link between dental and rheumatic pathology via citrullination [1–10].

We systematically reviewed data from literature focusing on inflammation and tissue-damaging aspects, oral microbiota, antibodies against bacteria and autoantibodies and treatment for both RA and periodontitis, aiming to explore the relationship between both diseases.

2. A closer look to periodontitis

2.1. Pathobiology of periodontitis

As a chronic immuno-inflammatory disease and a consequence of an infectious trigger that originally involves gingival soft tissue, periodontitis is classically characterized by the destruction of periodontium and surrounding connective tissue matrix [1–11]. It is a complex, dynamic and progressive condition, resulting from a continuing cross-talk between microbial challenge and host inflammatory and immune response [1–7].

The extent and severity of periodontitis, as well as disease staging covers a sequence of pathobiologic steps comprising gingivitis, plaque accumulation and chronic inflammation, colonization by periodontopathogenic anaerobes, loss of connective tissue attachments to teeth, bone resorption and, ultimately, tooth loss [1–10].

http://dx.doi.org/10.5772/65863

The oral cavity behaves as a perpetual source of infectious, generally nonpathogenic agents; however, subgingival microbiota may accumulate to shape this biofilm through particular settings, and favor networking between pathogens and host tissues, with or without direct dissemination [1–11].

The pathways underlying chronic periodontitis encompass for an intricate array of events, starting with gingival colonization by *P. gingivalis*, chronic inflammation, immune-mediated periodontal damage and alveolar bone loss, local citrullination, host immune response [1–11].

A schematic overview of the microbial and host-associated pathology in periodontal disease is represented in **Figure 1**.

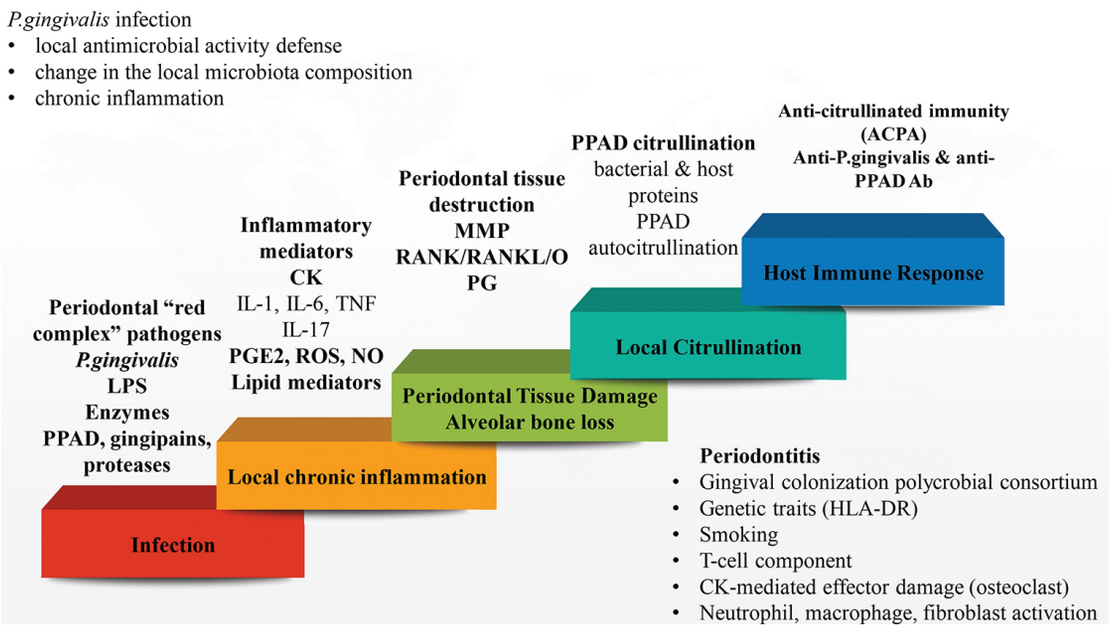

Figure 1. Sequence of events in chronic periodontitis.

It is widely recognized that the oral microbiota arising in a tolerant genetic background is involved in the initiation and extension of periodontal disease [1–12]. Several bacterial species, e.g., *P. gingivalis, Treponema denticola (T. denticola), Tannerella forsythia (T. forsythia)* and *Aggregatibacter actinomycetemcimtans*, the so-called red complex [1–12], remain of particular relevance as they are true pathogens and late colonizers of the oral biofilm, act synergistically and by co-aggregation with the support of attaching bacteria through specific adhesion molecules [1–10].

Further, *P. gingivalis* is able to release pathogen-associated molecular patterns, specifically lipopolissacharides (LPS), peptidoglycans, proteases and lytic enzymes, engaging local immune cell trafficking and activation—neutrophils (acting to protect the host from periodontal pathogens as the first-line defenders), macrophages (as potent antigen-presenting cells), T-cells and B-cells (perpetuating and amplifying inflammatory response and antibody synthesis) [1–11].

However, *P. gingivalis* escapes the local antimicrobial defense as a result of delayed neutrophil apoptosis and complement system manipulation with subsequent change in the gingival bacterial composition [11].

To better understand, *P. gingivalis* encourages the immune subversion by several strategies including: IL-8 inhibition, complement manipulation and toll-like receptor 4 (TLR4) antagonism, leading to impaired host defense. Symbiotic gingival microbiota with tissue homeostasis swaps to dysbiotic environment, with inflammation and bone loss as main attributes of periodontal disease [1, 8, 11, 12].

Locally recruited cells release a wide range of factors, such as pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-12, IL-11, IL-17), reactive oxygen species, prostaglandin E2, nitric oxide, and other inflammatory mediators in the gingival tissue and gingival crevicular fluid as well [1–5, 11–14]. Otherwise, anti–inflammatory cytokines including IL-10 and TGF-β1 are down regulated in active periodontal lesions, demonstrating an imbalance between pro- and anti-inflammatory systems in the periodontal microenvironment [1, 11].

Although the initial trigger of gingival inflammation is microbial, the cytokine-mediated damage is largely host-associated [1–10]. Hence, augmented TNF-α, IL-1β, IL-6, IL-11, and, particularly, IL-17 directly control the Receptor Activator of NF-κB/Receptor Activator of NF-κB Ligand/osteoprotegerin (RANK/RANKL/OPG) system and stimulate osteoclastogenesis through increasing RANKL expression reducing OPG synthesis in osteoblasts and stromal cells [1–11, 15]. Connective tissue matrix degradation is supplementary dependent on matrix metalloproteinases (MMPs) and other proteolytic enzymes discharged by resident activated fibroblasts [1, 10, 11].

Of particular interest, *P. gingivalis*-dependent protein citrullination and the immune response to the periodontal infective aggression involving both innate and adaptive immunity (e.g., anti-citrullinated immunity and IgG anti-*P. gingivalis* antibodies) additionally outline the complexity of pathogenic pathways in periodontitis [1–5, 7–10, 15].

Periodontis is a multifactorial condition, where environmental factors (including oral hygiene, gingival bacterial plaque, smoking, stress), and genetic polymorphism (HLA-DR alleles, IL-1 gene promoter, IL-6 and IL-10 genes) perform critical role in the expression of the disease [1, 4, 10, 11, 15, 16].

Recent data agreed that chronic periodontitis is a risk factor for many multisystem diseases including rheumatoid arthritis and other auto-inflammatory rheumatic conditions, cardio and cerebrovascular disease (atherosclerosis, myocardial infarction, stroke), diabetes, osteoporosis, respiratory and neurodegenerative disorders, adverse pregnancy outcomes [1, 17, 18]. In fact, locally exacerbated and ongoing systemic inflammation, specific tissue damage, mutual triggers (smoking, iatrogenic factors) acting in a genetic vulnerable individuals (HLA-DRβ1) uphold a modulating bidirectional relationship between periodontitis and the above mentioned entities [1–18].

It is obvious that chronic periodontitis remains an authentic infection of the oral cavity; biofilm-associated specific microorganisms are essential but not sufficient, as the bacterial eradication does not spontaneously manage to resolution of periodontitis [1–18].

http://dx.doi.org/10.5772/65863

2.2. *Porphyromonas gingivalis* as a key player in periodontitis

Chronic periodontitis is, therefore, typically initiated by the colonization of dental plaque by a core set of periodontal pathogens, specifically *P. gingivalis, T. forsythia* and *T. denticola*, documented as the "red complex", prototype of polybacterial pathogenic consortium in periodontitis [1–5, 7–11, 19].

P. gingivalis, a leading microorganism in this dysbiotic setting, is a gram-negative anaerobic bacteria, involved in the onset of inflammation and tissue destruction during periodontal disease [1–11]. It is ordinarily found in small number in a healthy oral cavity [11], but the pathology occurs when *P. gingivalis* binds to and accumulates on the tooth surface, leading to the development of a mixed biofilm, the expansion of the bacteria into the gingival sulcus and the formation of a periodontal pocket [11, 19].

P. gingivalis is an outstanding example of a bacteria able to shape the periodontal microenvironment and to destabilize the homeostatic immune system endorsing chronic inflammation and tissue damage as well [11].

At least four mechanisms currently advocate for its essential role in the pathobiology of periodontal disease: (i) the release of specific virulence factors such as specific lipopolysaccharide (LPS), fimbrae, hemagglutins and several enzymes, mainly cysteine proteases (gingipains), but also collagenase, gelatinase, hyaluronidase promoting a chronic inflammatory setting and local invasion [2, 3, 11, 20]; (ii) the expression of peptidyl arginine deiminase (PAD) involved in tissue citrullination, loss of tolerance against neo-epitopes and subsequent activation of adaptive immune response [1, 2, 3, 20]; (iii) auto-citrullination of its own PAD [1, 2, 3, 11, 20]; and (iv) enable other co-aggregating pathogenic bacteria to remain in the periodontal tissue [2].

P. gingivalis expresses atypical LPS, proceeding either as a weak TLR4 agonist or even a TLR4 antagonist, enabling the colonization and invasion of periodontal pockets as it becomes immunologically silent [1, 2, 8, 11, 21]. Furthermore, *P.gingivalis* invades gingival epithelial cells via binding through its fimbriae to β1 integrin on the host epithelial cell surface [4, 5, 11] and blocks apoptosis through the PI3K/Akt and JAK/Stat pathways, allowing intracellular bacterial proliferation [11].

The true virulence of *P. gingivalis* is, however, associated with its proteolytic enzymes, particularly extracellular arginine and lysine-specific cysteine endopeptidases (gingipain R and gingipain K, respectively) [1–5, 11]. Gingipains are skilled to facilitate the evasion of host defense and cause tissue injury by activation of MMPs (1, 3, 9) and further degradation of host proteins (laminin, fibronectin and collagen) [1, 2, 8 11, 22–24]. Moreover, these enzymes are responsible for the resistance of *P. gingivalis* killing by complement [1, 2, 8, 11]. Remarkably, the degradation of microbial peptides by gingipains allows other pathogenic bacteria co-aggregating with *P. gingivalis* to persist in the gingiva [2, 8, 11, 15, 20, 25]. Finally, gingipains affect proinflammatory signaling pathways by cleavage and activation of the proteinase-activated receptor-2 on human neutrophils [2, 11, 15, 20]. Futile attempts by the host immune response to eliminate infection subsequently lead to connective tissue damage, including alveolar bone resorption [22].

P. gingivalis is a particular periodontal pathogen that expresses endogenous peptidyl-arginine deiminase (PPAD), a citrullinating enzyme bearing potential to generate antigens driving autoimmunity in susceptible individuals [1, 2, 8, 10, 11].

It is worth mentioning that the switching of a charged arginine residue to an uncharged citrulline results in evident, irreversible posttranslational protein modifications, meaning changes in the three-dimensional conformation and abnormal function [8, 10, 17]. Citrullinated antigens as neo-epitopes in the periodontal tissues may selectively activate adaptive immune response and break the self-tolerance leading to severe aggressive periodontitis, anti-cyclic citrullinated peptides, anti-*P. gingivalis* antibodies as well, and, potentially, to the development of RA in genetically predisposed hosts [1–3, 20, 25].

PAD-mediated citrullination is also responsible for evading host defense against *P. gingivalis* by two additional mechanisms: generation of ammonia that result in a favorable microenvironment for anaerobic bacteria and inactivation of certain chemokines contributing to neutrophil recruitment into the gingiva [8, 10, 11, 17].

Besides, *P. gingivalis* stimulates a true "local chemokine paralysis" by inhibiting the expression of IL-18 on epithelial cells [8, 11], delaying the traffic of neutrophils and, therefore, permitting its persistence and/or proliferation in the periodontal tissue with subsequent modification of the subgingival microbiota [11, 25].

2.3. *P. gingivalis* peptidyl-arginine deiminase (PPAD) *versus* peptidyl-arginine deiminase (PAD) biology

There is accumulating evidence to outline the citrullination status and biology of PPAD *versus* human PAD, supporting the hypothesis that PPAD is a reliable challenger for inducing autoimmunity, with particular relevance to the pathogenesis of RA [1, 2, 10, 11, 17, 20, 22, 26, 27].

This apparently distinctive bacterial enzyme is effective in generating citrullinated proteins (bacterial and human) and, furthermore, has the ability to autocitrullinate, eliciting the loss of immune tolerance and synthesis of autoantibodies in susceptible individuals [1–5, 7–11, 22].

To date, five isoforms of human PADs (PAD1, 2, 3, 4/5, and 6) are described, with specificities for different tissues and different physiological functions [2, 3, 10]; however, none of them present strict homology with bacterial PAD [1, 2, 10, 11, 17, 27], and only PAD2 and PAD4 are expressed at the synovial level and involved in RA [1, 3, 10, 26].

The main differences between human and bacterial PAD focus on the mechanism of activation and substrates undergoing citrullination [1, 10, 11]. Thus, PPAD is a calcium-independent enzyme that becomes active at higher pH that PAD; its action is facilitated by the co-localization with arginine-specific gingipains in the outer membrane of *P. gingivalis* [1, 2, 10, 11, 20, 25]. PPAD act specifically on C-terminal arginine residues and free arginine [1, 2], events enabled by the proteolytic activity of gingipains. In fact, we talk about a two-step process in the inflamed-infected periodontal sites, initiated by cysteine protease gingipains that cleave protein chains and expose the C-terminal arginine, facilitating the secondary intervention of PPAD [1, 2, 10, 11, 25].

http://dx.doi.org/10.5772/65863

Other substrates citrullinated by PPAD include peptides resulted from fibrinogen and α-enolase degradation by gingipains [2, 10], fibrin and vimentin, bradykinin with the potential impairment of kinin proinflammatory activity [2, 10, 20, 25], and the C-terminal arginine residue of the epidermal growth factor influencing its biologic activity [2, 10, 25, 27, 28].

Finally, PPAD allows, either directly or indirectly (via enhancement of inflammatory reactions and release of host PADs), the abnormal citrullination of bacterial and human proteins with the assembly of the so-called cryptic-epitopes and subsequent antibody production [1, 2, 10, 11, 20, 25].

2.4. PPAD and PAD autocitrullination

Although PPAD preferentially citrullinates different bacterial and/or host peptides bearing C-terminal arginine, it becomes clear that this enzyme may undergo autocitrullination and, hence, stimulate a specific pattern of autoimmunity and request for autoantibody response in permissive genetic background (carriers of HLA-DRB1 shared epitope) [2, 10, 20]. There is a heightened immune response to *P. gingivalis* and IgG specifically targeting autocitrullinated PPAD in chronic periodontal disease and rheumatoid arthritis which could perpetuate the immune response through epitope spreading and cross-reactivity with citrullinated human proteins suggesting a potential mechanistic linkage between the two disorders [10, 11, 25, 29, 30]. Of interest, PAD4 also experiences autocitrullination, and antibodies recognizing this isoform of human PAD embrace predictive value in RA [10, 11, 26, 27, 31].

To summarize, the infection with *P. gingivalis* triggers a broad spectrum of local and systemic inflammatory, destructive and immune events in susceptible individuals. Strategic steps in the complex pathobiology of periodontitis comprise early release of a true arsenal of specialized virulence factors and bacteria-danger signals (LPS, fimbriae, peptidoglycan, various proteolytic enzymes) exerting both direct and indirect effects (via stimulation of inflammatory and immune pathways, release of host PAD), followed by aberrant PPAD-dependent citrullination of different substrates such as host-derived and bacterial proteins, as well as PPAD-autocitrullination, with subsequent generation of criptic epitopes and autoantibody synthesis. Finally, the immune subversion endorses loss of tolerance to structurally similar host proteins and outcomes the induction of anti-cyclic citrullinated antibodies suggesting the relationship between chronic periodontitis and rheumatoid arthritis [1, 2, 10, 13, 17, 19, 20, 25].

3. Role of citrullination in rheumatoid arthritis development

Citrullination is a posttranslational modification of proteins at arginine residues reported in a wide range of tissues and settings, holding relevant physiologic as well as pathologic implications [10, 17, 27, 32]. Although considered a critical event in different inflammatory conditions, currently available data emphasize the link between citrullination and autoimmune diseases, suggesting that immunity towards citrullinated self-proteins rather than citrullination itself is a specific event in RA [10, 17, 27].

3.1. Citrullination and inflammation

Abnormal citrullination of endogenous proteins is typically acknowledged as an initial, tactical process in the complex pathobiology of RA, driving the induction of altered self-epitopes and extensive autoimmune response [10, 17, 27].

Moreover, immunogenicity of these new antigens explains the presence of antibodies against citrullinated peptides (ACPA) considered not only diagnostic biomarkers for RA and prognostic factors for severe aggressive disease, but also consuming a pathogenic role [10, 17, 27]. Nevertheless, only individuals with definite HLA polymorphisms, such as the conserved region of HLA-DRB1 alleles are at risk to recognize as "nonself" such citrullinated proteins and to develop RA [1, 2, 10, 17, 27].

Along with glycosylation and carbamylation, citrullination is basically involved in many physiological processes in a variety of tissues, biochemical enzymatic reactions leading to structural and functional protein/peptide modification [2, 10, 17, 27]. Conversely, dysfunctional posttranslational protein modifications are often reported during autoinflammatory pathology, particularly RA, evading the immunological tolerance and stimulating a specific profile of humoral response [2, 10, 17, 26, 27].

As mentioned before, citrullination or deamination strictly encompass for a change of arginine with citrulline, meaning that an imine nitrogen of arginine-residues is replaced by an atom of oxygen; accordingly, histone modification, genomic regulation and neutrophils extracellular trap (NET) formation are described and engaged in development of newly citrullinated antigens [10, 17, 27].

It is well-known that citrullination constantly requires the activation and intervention of PAD-family enzymes at intra and/or extracellular levels in a Ca^{2+}-dependent manner, and only two out of the five human PAD subtypes (PAD 2 and PAD4) are relevant for RA based on their expression in joints, immune cells, neutrophils and mast cells [1, 10, 11, 12, 17, 26, 27]. Thus, PAD-mediated citrullination could be easily classified as a basic cellular damage but also an inflammatory process occurring in a range of inflammatory backgrounds such as synovial tissue, gingival and periodontal sites and lungs, challenging local immunity [10, 17, 27].

On the other hand, recent advances in understanding the pathophysiology of chronic periodontal infection with *P. gingivalis*, and the potential connection between periodontitis and systemic disorders including RA, have reemphasized the role of this periodonthopathic microbe as one of the risk factors for RA in a permissive genetic context [1–11, 17, 27].

P. gingivalis is the only known periodontal bacteria in the gingival microbiota that expresses a PPAD able to initiate and perpetuate a gradual autoimmune process through epitope-spreading by peptide citrullination (bacterial, PPAD itself as a citrulllinated bacterial protein), cross-reactivity with citrullinated human proteins and ACPA synthesis [1, 2, 10, 11, 25].

The break of tolerance to one citrullinated epitope predisposes to break of tolerance to additional citrullinated epitopes; the initial mechanism might be more related to recognition of citrullinated antigen per se than to a particular citrullinated autoantigen [10, 11, 26, 32, 33].

3.2. Smoking, citrullination and rheumatoid arthritis

Environment-triggered citrullination (smoking, bacterial infections) in articular and extra-articular locations essentially progress to specific immunity and disease in genetic predisposed individuals [1, 2, 10, 12, 16, 32, 34, 35]. Smoking is a well-known risk factor for RA, particularly, in ACPA-positive subsets. Cigarette smoking leads to a sequence of events responsible for local increase in PAD enzyme expression and consequent generation of protein citrullination in the lung [10, 12, 17, 27]. Chronic exposure to self-citrullinated epitopes could further contribute to the loss of immune tolerance and gradual occurrence of humoral immune response towards some of the citrullinated autoantigens (ACPA) [10, 17, 27]. However, smoking and other risk factors might lead to breaking of immune tolerance only in the presence of genetic risk factors for ACPA positive RA [10, 12, 17, 26, 27, 36].

3.3. Anti-citrullinated proteins/peptide antibodies (ACPA) pathobiology

ACPAs, the autoimmune signature of RA, are sensitive and specific diagnostic, prognostic and therapeutic biomarkers in RA; they are detected from very early phases of the disease, up to a decade prior to the RA clinical onset, and feature a dynamic correlation with RA severity, clinical outcomes and efficacy of synthetic and biologic therapies [10, 37, 38]. In fact, ACPAs are a family of partly cross-reactive antibodies which target citrullinated self-proteins and peptides abundant in inflamed joints, such as fibrinogen, fibronectin, vimentin and vinculin, β-enolase, histone, biglycan, clusterin, collagen type II, keratin. So far, 53 such citrullinated members are identified, an assembly called "citrullinome" [10, 12, 17, 27].

According to the ACPA status, RA could be classified in two distinct clinical phenotypes with particular genetics, risk factors, immunopathology, clinical and treatment outcomes; thus, ACPA-positive RA is defined by a specific genetic (HLA-DRB1*0401 and *0404)- environmental interface (e.g., smoking and *P. gingivalis* infection), higher disease severity (erosive RA, extra-articular involvement, comorbidities) and poor remission rates. Besides, high ACPA titers could predict clinical response with B-cell depletive agents (rituximab) or selective co-stimulation modulators (abatacept), independently of disease activity and, therefore, might help to define therapeutic RA profiles [10, 11, 16, 17, 27, 28, 36].

Interestingly, ACPA specificities may also account for distinctive clinical RA subtypes: anti-citrullinated vimentin antibodies may be better prognostic factors for radiographic progression, while anti-citrullinated enolase antibodies predict clinical outcomes [10, 17, 27].

ACPAs are detected as antibodies against cyclic citrullinated proteins (anti-CCP antibodies) which are detectable by specific assays in RA patients, and their screening performance largely varies with different tests: sensitivity and specificity significantly improved with third-generation assays, as well as the ability to identify those subjects with undifferentiated arthritis who are likely to develop RA [10, 17]. Conversely, second-generation tests are classically more specific for longstanding, established disease [10, 17, 39].

The exact molecular pathways of anti-citrullinated immunity in RA are still obscure, but it is clear that ACPAs encourage the perpetuation of synovial inflammation via binding to citrullinated proteins positioned in the cellular membrane, attached to a variety of cellular

receptors (such as TLR4 or FcγR) or incorporated in NETs [1–4, 10, 11, 17]. Furthermore, complement binding and activation may enhance local inflammation [7, 12, 17, 27].

ACPAs are constantly produced in the inflamed synovial microenvironment by locally activated B cells [17, 27] and stimulate TNFα production, as well as direct bone injury by osteoclast activation [6, 10, 17, 27, 39, 40].

Overall, the effector functions of different well-defined ACPA may adjust according to antibody specificities. Thus, reactivity towards citrullinated vimentin as well as anti-cartilage-specific protein collagen II antibodies directly bind to osteoclast surface and modulate their activation, determining subchondral bone erosive lesions and osteoporosis [10, 12, 40]. On the other hand, antibodies to autoantigenic enolase and histones focus on local inflammation [10, 12, 17, 27], as ACPAs are able to induce NETs.

3.4. The paradigm of citrullination and ACPA in the development of ACPA positive rheumatoid arthritis

The environmental exposure (such as smoking, silica and other nanomaterials of air pollution, bacterial infection, e.g., *P. gingivalis*) and the genetic determinants (MHC class II alleles) enable abnormal citrullination and support immunity against citrullinated proteins in certain extra-articular sites (lung, periodontal tissue). The relationship between the emergence of local ACPAs as the first sign of autoimmunity and RA is further supported by the documentation of shared citrullinated peptides in the lungs, periodontal sites and joints as potential ACPA epitope bearing proteins [10, 17, 27].

A second event might promote aberrant synovial citrullination, local impaired immunity, generation of ACPA for several immune-dominant citrullinated peptide, chronic inflammation and tissue-specific damage [10, 17, 27].

4. The biological link between periodontitis and rheumatoid arthritis

Continuing periodontal disease as a trigger for chronic arthritis in susceptible individuals via dysregulation in oral microbiota and host immune barriers is a reliable, but still debatable concept [1, 2, 8, 10–12]. The old paradigm indicates that RA could be a consistent risk factor for chronic periodontitis: impaired periodontal health labels the multifactorial and synergistic result of compromised joint functionality (hand as well as temporomandibular joint), oral dryness (secondary Sjogren's) and specific RA medications [8].

In contrast, newer theories emphasize that periodontal disease is a risk factor for RA: both are multifaceted disorders with shared pathogenic mechanisms such as local and systemic excess of inflammation, irreversible bone injury, aberrant activation of the immune system with an extra dose of autoimmunity and a common genetic background [1–5, 8, 41–45].

http://dx.doi.org/10.5772/65863

4.1. Evidences relating periodontitis and rheumatoid arthritis

Substantial amount of research trying to clarify the potential relationship between RA and periodontitis was published during the last decade [1–13]. Nevertheless, the true prevalence, causality, significance, related factors (e.g., smoking habits, oral hygiene, ACPA positivity), together with therapeutic intervention (periodontal host modulation therapy, synthetic remissive drugs, biologics) to mitigate both RA and periodontal disease are still controversial [1–13, 17, 27].

Overwhelming evidence coming from cross-sectional studies [1–13, 10, 40, 46–48] showed a statistically significant correlation between RA and periodontitis (prevalence and/or severity); nevertheless, other cohort-based or case-control studies noticed no association between oral health and rheumatic inflammatory pathology [1, 2, 10, 12]. The conflicting reports may be explained by differences between study populations, sample size, adjustments for confounders (age, gender, race/ethnicity, smoking status, RA activity and medication) and lack of uniformity in disease classification criteria for periodontal disease [49].

The probability of periodontitis among RA is higher compared to healthy individuals [1–4, 8, 47], while the severity greater [1–4, 8, 15, 47], meaning that subjects diagnosed with RA experience more periodontal disease and more periodontal destruction [1, 8, 15]. Furthermore, moderate to severe periodontitis is characteristically described in different settings of RA [1, 8], and vice-versa, higher RA prevalence among patients with advanced periodontitis [1, 8, 15, 47, 49]. Both early and established RA are characterized by substantial periodontal disease compared with presumably healthy non-RA controls [1–4, 6, 8, 44, 45]: higher prevalence of self-reported periodontal symptoms [8], significant more gingival bleeding on probing [1–4, 6, 8], a greater number of missing teeth [1–4, 6, 8], deeper periodontal pockets [1–4, 6, 8], more clinical attachment loss [1–4, 6, 8] and increased alveolar bone injury [1–4, 6, 8] versus healthy controls with comparable oral hygiene [1–4, 6, 8, 44, 45].

More specifically, a meaningful positive correlation between measures of RA activity and extent and severity of periodontitis was reported: high disease activity (DAS28 scores) is generally demonstrated in RA with aggressive periodontitis as compared to RA without or with moderate periodontitis, even after adjusting for multiple confounders [4, 8, 47].

A systematic review of cross-sectional trials further strengthens the evidence addressing periodontitis in relation to autoimmunity damage in RA. Overall, significantly higher ACPA, rheumatoid factor and antibodies to *P. gingivalis* were described among RA with periodontitis than those without periodontal disease [4, 8, 11, 47], whereas increased alveolar bone loss was significantly associated with ACPA positivity in the same patient population [4]. Similarly, detailed analysis of ACPA specificities (citrullinated vimentin and histone) showed increased levels in RA associated with both moderate and high alveolar loss, without differences based on smoking status [4, 15, 16, 26, 48–50]. It seems that periodontitis is a strong predictor of ACPA positivity in RA [8], whereas IgG and IgM ACPA subtypes are highly associated with antibodies against *P. gingivalis* [2, 3, 8, 29]. Additionally, in refractory RA with periodontitis the most powerful anaerobes identified in synovial fluid are *P. intermedia, P. gingivalis* and *T. denticola* [1, 40, 41]. However, no difference in ACPA or rheumatoid factor levels for RA

participants with mild periodontal lesions as compared to moderate or severe periodontitis were found among other studies, suggesting that ACPA status might not influence the prevalence and severity of periodontal disease [1, 8, 11, 49].

Regarding smoking as a risk factor for both conditions, subgroup analysis showed an association between RA and periodontitis irrespective to smoking behavior [4, 6, 8, 15, 16, 48, 49]; increased risk of periodontitis was demonstrated in nonsmoking RA [1, 6, 8, 11].

In particular, only a small number of studies focused on periodontitis as a primary event, occurring before clinical onset of RA *versus* periodontitis as comorbidity, described after the diagnosis of rheumatic condition [1, 8, 11].

Finally, effective treatment strategies for periodontal disease (e.g., nonsurgical treatment) on RA activity and systemic inflammation are commonly reported [1, 3, 4, 50, 51].

4.2. A parallel between chronic periodontal disease and rheumatoid arthritis

Exploring the association between chronic periodontal disease and RA has demonstrated striking similar immunological, biological and genetic underlying processes [1, 2, 4, 12, 22], although apparently totally different etiologies (autoimmune RA, infective periodontitis respectively) [10]. **Figure 2** offers a detailed synopsis of similarities between RA and periodontitis.

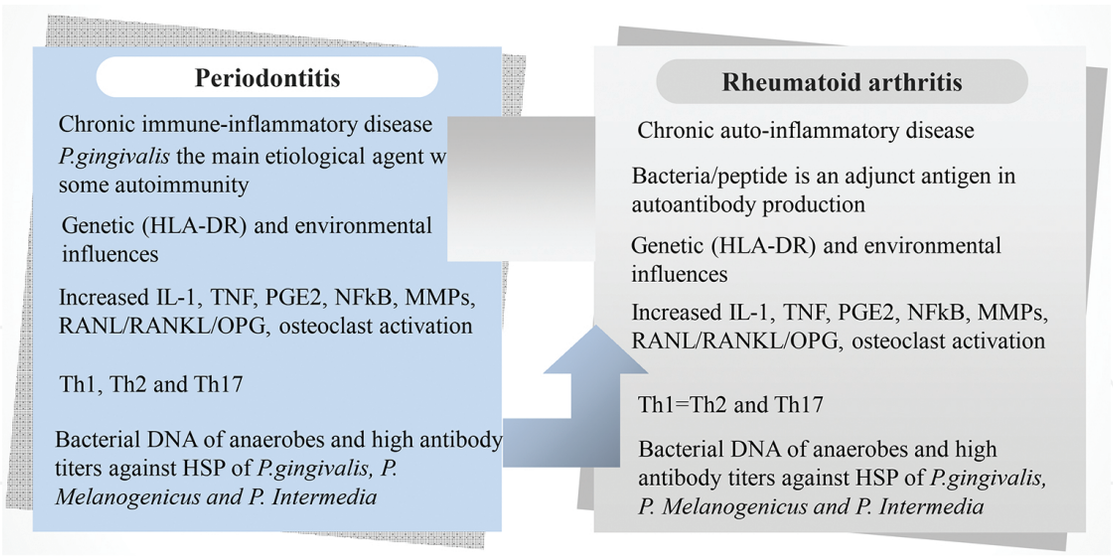

Figure 2. Similarities between PD and RA pathobiology.

Both are complex multifactorial disorders, characterized not only by a dysfunction of basic inflammatory and tissue destructive mechanisms, but also by an altered adaptive and innate immune response in individuals at risk (genetic traits) [1, 2, 8, 10, 12, 22].

The excess of local (periodontal tissue and gingival crevicular fluid in periodontitis, synovial microenvironment in RA) along with systemic chronic inflammation is driven by an imbalance

http://dx.doi.org/10.5772/65863

between pro-inflammatory and anti-inflammatory cytokines, with persistent up-regulated pro-inflammatory signaling pathways (mainly IL-1, IL-6, TNFα, NF-kB) and higher amounts of inflammatory mediators including reactive oxygen species, nitric oxide and lipid mediators [1–3, 8, 10–12, 22]. In addition, altered connective tissue and bone homeostasis with irreversible damage of collagen-rich structures (gingiva, periodontal ligament and alveolar bone in periodontitis, subchondral bone and cartilage in RA) is essentially related to augmented activity of collagenolytic matrix metalloproteinases and other enzymes (elastase, bacterial cysteine proteases, neutrophil associated enzymes), but also to overexpression of the RANK/RANKL/OPG system [1–3, 8, 10, 12, 13, 45].

The validity of the relationship between periodontitis and RA is, furthermore, supported by a particular genetic predisposition and related environmental risk factors (e.g., smoking) [1, 8, 10, 12]; both entities share a common genetic profile (shared epitope HLA-DRB1 alleles) [1, 10, 12], while polymorphism of genes encoding inflammatory cytokines as well as IL-1 combined risk alleles which may cause a synergistic effect on bone destruction in joints and the periodontium might also confer susceptibility for RA and periodontitis [1, 8, 10, 12, 15, 16].

Finally, abnormal PAD and PPAD-mediated citrullination of the synovial and host periodontium peptides/proteins (vimentin, keratin, α-enolase), respectively, with sequential loss of tolerance against neo-epitopes account for altered local and systemic immune reactions in susceptible patients with either periodontitis or RA; the generation of citrullinated new autoantigens and patterns of antibody response by ACPA, anti-autocitrullinated PPAD, anti-autocitrullinated PAD4 and anti-heat shock proteins of *P. gingivalis* (anti-hsp70) antibodies are frequently encountered in both RA and periodontitis [1, 10, 12, 15, 25, 30, 45].

Overall, gingival citrullination and local induction of ACPA, as well as cross-reactivity between antibodies to *P. gingivalis* and ACPA may explain the link periodontitis—RA [1, 10, 12, 27].

4.3. Hypothetical model of biological link Between rheumatoid arthritis and periodontitis

A potential scenario exploring the relation between periodontitis and RA could be depicted as follows:

- oral infection with *P. gingivalis* may induce a Th17 polarization with subsequent activation of Th17 signaling pathway, synthesis of pro-inflammatory cytokines (preferentially IL-1β, IL-6, IL-22, TNF-α, TGFβ and IL-23), expression of PPAD with atypical PPAD- and PAD-dependent citrullination of gingival proteins, bacterial peptides and PPAD as well, synthesis of specific antibodies such as ACPA, anti-citrullinated PPAD and anti-*P. gingivalis* antibodies [1, 4, 8, 10–13, 19, 52];
- periodontopathic microbial biofilm and its metabolic products (lipopolysaccharides, matrix degrading enzymes and endotoxins) originally stimulate a localized inflammatory-destructive response branded by augmented levels of tissue destructive proteinases (MMP 8, 9, 13 and neutrophil elastase) and RANK/RANKL/OPG system, as well as resident cells activation (osteoclasts, fibroblasts) [1, 4, 8, 12];

- systemic inflammation and immune dysregulation particularly autoimmunity targeting self-citrullinated synovial peptides delineate one of the first events in RA [1, 4, 8, 10, 12].

Figure 3 presents the paradigm of RA—periodontitis pathogenic link.

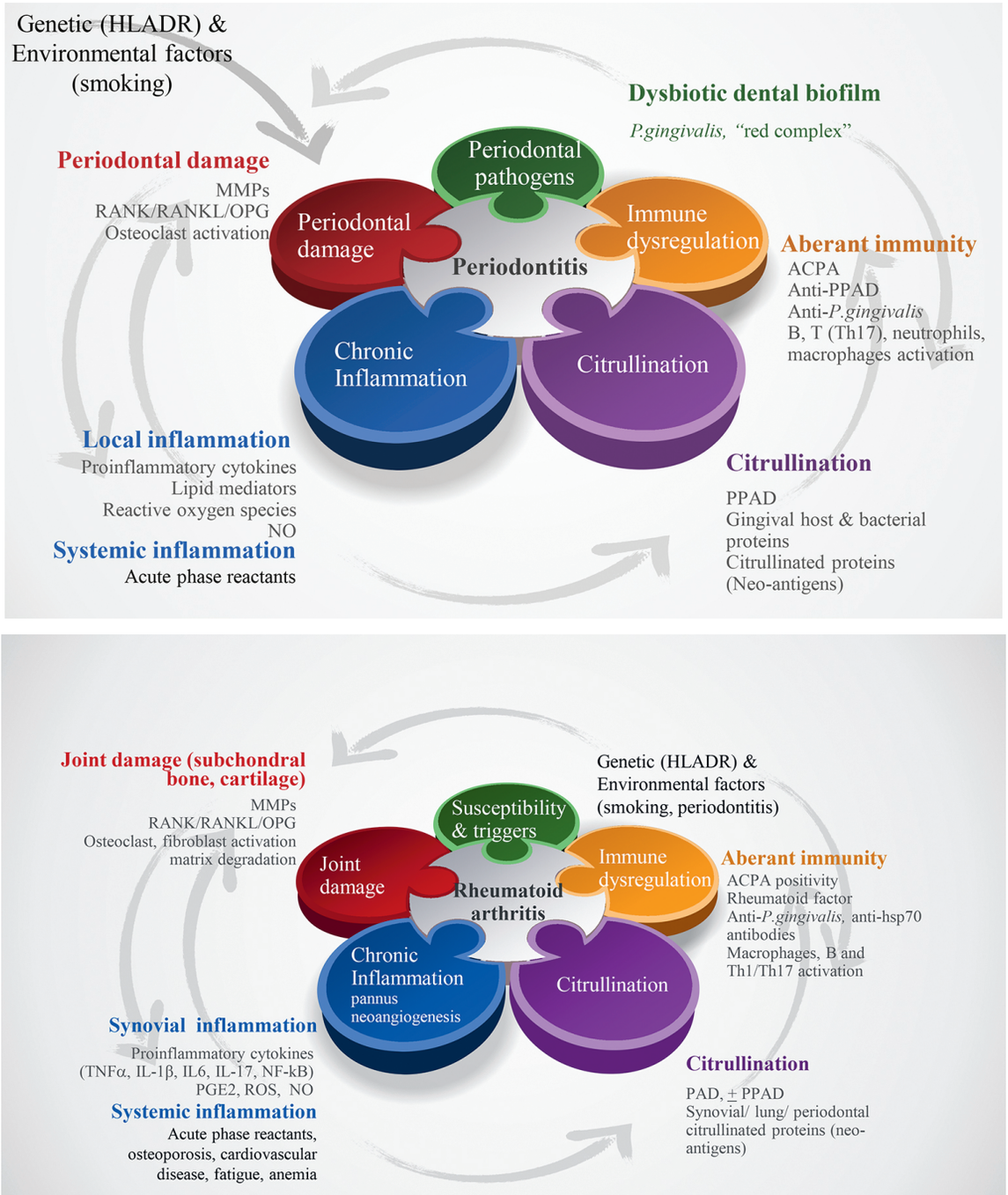

Figure 3. The paradigm of RA—periodontitis pathogenic link.

A 'two-hit' model for the link between periodontitis and systemic diseases including RA have already been proposed by Gloub et al. [4] and recently modified, evoking a sharp cascade of

http://dx.doi.org/10.5772/65863

events: induction of severe chronic periodontitis by local and systemic factors in relation to RA ('first hit'), and their mitigation by periodontal host modulating therapy ('second hit') [4].

4.4. Therapeutic interferences in rheumatoid arthritis and chronic periodontitis

Current evidences suggests that periodontal treatment may influence clinical outcomes of RA and vice-versa, stipulating the potential advantage of host-modulating therapy to concomitantly control both disorders [1, 4, 8, 48, 50, 53–57].

4.4.1. Effects of therapy for periodontitis on rheumatoid arthritis disease activity and systemic inflammation

It was advocated that specific therapies for periodontitis not only improve disease activity and severity in RA by removing periodontal infection and gingival inflammation, but also improve patient response to therapeutic drugs [1, 8, 50, 53, 54].

Thus, nonsurgical periodontal therapy was directed to improve both signs and symptoms of active RA as well as periodontal status [1, 8, 12]. Similarly, advanced periodontal treatment with scaling and root planning significantly ameliorated gingival infection and severity of periodontitis, while promoting consistent reduction in acute phase reactants, mainly erythrocyte sedimentation rate, in the RA population [1, 8, 12, 53, 54]. The impact of periodontal treatment on RA seems to be greater in patients with substantial amount of systemic inflammation, particularly if periodontitis intervention therapy combined with adjunctive periodontal host-modulating therapy [4, 12, 53, 54].

Furthermore, a positive influence on RA activity scores, rheumatoid factor and ACPA levels, but also on anti-*P. gingivalis* antibodies was reported following supportive periodontal therapy in patients having concomitant RA and chronic periodontitis [1, 12, 52, 54–56].

The consequences of therapy for periodontal disease on RA status actually reflect on the decrease in systemic inflammation, removal of joint exposure to the infectious trigger and the decline in microbial immune subversion [1, 8, 12].

4.4.2. Effects of conventional therapy for rheumatoid arthritis on periodontal status

On the other hand, different authors concluded that early aggressive RA management with synthetic disease modifying anti-rheumatic drugs (DMARDs) and/or biologic agents aiming to achieve and maintain disease remission according to treat-to-target strategies might also restrict periodontal damage in active periodontitis [1, 8, 12, 54].

It is widely accepted that systematic DMARDs ameliorate periodontal disease burden in RA patients with periodontitis, i.e., they decrease gingival inflammation and periodontal destruction [1, 8, 12, 54]. Moreover, glucocorticoids and TNF antagonists are able to clinically improve periodontal disease in RA patients [1, 8, 12, 54]. Anti-cytokine therapy, specifically anti-TNF agents, may play dual role on synovitis as well as periodontal disease [1, 8, 12, 54, 55], reducing inflammation and mitigating both conditions [1, 4, 8, 12]. However, the role of TNF inhibition on periodontitis outcomes in the absence of periodontal treatment is still controversial [1, 8, 12].

5. Conclusions

There is a significant interplay between periodontitis and rheumatoid arthritis as supported by emerging evidences. Despite common T cell activation, the imbalance between pro-inflammatory and anti-inflammatory cytokine profile, citrullination of endogenous proteins and the resultant bone destruction in specific environments (synovium and gingival tissue), further research is required to assess the exact mechanisms and causative link, as well as to define top therapy.

Author details

Codrina Ancuta[1*], Cristina Iordache[2], Eugen Ancuta[3] and Claudia Mihailov[4]

*Address all correspondence to: codrina_ancuta@yahoo.com

1 2nd Rheumatology Department, Clinical Rehabilitation Hospital, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

2 Ergonomics Department, School of Dentistry, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

3 Research Department, "Elena Doamna" Clinical Hospital, Iasi, Romania

4 2nd Medical Department, Clinical Port Hospital of Constanta, Faculty of Medicine, 'Ovidius' University of Constanta, Romania

References

[1] Joseph R, Jose Raj MG, Sundareswaran S, et al. Does a biological link exist between periodontitis and rheumatoid arthritis? World J Rheumatology. 2014;4(3):80–87.

[2] Koziel J, Mydel P, Potempa J. The link between periodontal disease and rheumatoid arthritis: an updated review. Curr Rheumatol Rep. 2014;16:408.

[3] Batool H, Afzal N, Shahzad F, Kashif M. Relationship between rheumatoid arthritis and chronic periodontitis. J Med Radiol Pathol Surg. 2016;2:11–14.

[4] Payne JB, Gloub LM, Thiele GM, et al. The link between periodontitis and rheumatoid arthritis: a periodontist's perspective. Curr Oral Health Rep. 2015;2:20–29.

[5] Araujo VM, Melo IM, Lima V. Relationship between periodontitis and rheumatoid arthritis: review of the literature. Mediat Inflam. 2015;259074:1–15.

[6] Fuggle NR, Smith TO, Kaul A, Sofat N. Hand to mouth: a systematic review and metaanalysis of the association between rheumatoid arthritis and periodontitis. Front Immunol. 2016;7(80):1–10.

[7] Saini R. Periodontitis and rheumatoid arthritis: inflammatory relationship. J Pharm Bioallied Sci. 2011;3(3):464–465.

[8] Bingham CO. Round 34: periodontal disease and rheumatoid arthritis [Internet]. 2010 [Updated: 2011]. Available from: http://www.hopkinsarthritis.org/physician-corner/rheumatology-rounds/r. [Accessed: 01-aug-2016]

[9] Detert J, Pischon N, Burmester GR, et al. The association between rheumatoid arthritis and periodontal disease. Arthritis Res Ther. 2010;12:218 (1–7).

[10] Valesini G, Gerardi MC, Iannuccelli C, et al. Citrullination and autoimmunity. Autoimmun Rev. 2015;14(6):490–497.

[11] Hussain M, Stover CM, Dupont A. P. gingivalis in periodontal disease and atherosclerosis—scenes of action for antimicrobial peptides and complement. Front Immunol. 2015;6(45):1–6.

[12] Hein C. A closer look at the association between periodontal disease and rheumatoid arthritis. Dimens Dent Hyg. 2008;6(3):30–33.

[13] van Dyke TE. Commentary: periodontitis is characterized by an immuno-inflamatory host-mediated destruction of bone and connective tissues that support the teeth. J Periodontol. 2014;85:509–511.

[14] Gümüş P, Buduneli E, Başak B, et al. Gingival crevicular fluid, serum levels of receptor PArheumatoid arthritis and osteoporosis and with periodontal disease. J Periodontol. 2013;84(11):1627–1637.

[15] Kobayashi T, Yoshie H. Host responses in the link between periodontitis and rheumatoid arthritis. Curr Oral Health Rep. 2015;2:1–8.

[16] Klareskog L, Malmström V, Lundberg K, et al. Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. Semin Immunol. 2011;23:92–98.

[17] Catrina AI, Ytterberg AJ, Reynisdottir G, et al. Lungs, joints and immunity against citrullinated proteins in rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:645–653.

[18] Badran Z, Strillou X, Verner C, et al. Periodontitis as a risk factor for systemic disease: are microparticles the missing link? Med Hypotheses. 2015;84(6):555–556.

[19] Mysak J, Podzimek S, Sommerova P, et al. Porphyromonas gingivalis: Major periodontopathic pathogen overview. J Immunol Res.2014;2014:476068.

[20] Maresz KJ, Helvard A, Sroka A, et al. Porphyromonas gingivalis facilitates the development and progression of destructive arthritis through its unique bacterial peptidylarginine deiminase (PAD). PLoS Pathog. 2013;9:81003627.

[21] Hajishengallis G, Liang S, Payne MA, et al. Low-abundance biofilm species orchestrates inflammatory periodontal disease through the commensal microbiota and complement. Cell Host Microbe. 2011;10:497–506.

[22] Leech MT, Bartold PM. The association between rheumatoid arthritis and periodontitis. Best Pract Res Clin Rheumatol. 2015;29:189–201.

[23] Scher JU, Abramson SB. Periodontal disease, Porphyromonas gingivalis, and rheumatoid arthritis: what triggers autoimmunity and clinical disease? Arthritis Res Ther. 2013;15:122(1–3).

[24] Scher JU, Bretz WA, Abramson SB. Periodontal disease and subgingival microbiota as contributors for rheumatoid arthritis pathogenesis: modifiable risck factors? Curr Opin Rheumatol. 2014;26:424–429.

[25] Konig MF, Paracha AS, Moni M, et al. Defining the role of Porphyromonas gingivalis peptidylarginine deiminase (PPAD) in rheumatoid arthritis through the study of PPAD biology. Ann Rheum Dis. 2015;74(11):2054–2061.

[26] Harvey GP, Fitzsmmons TR, Dhamarpatni AA, et al. Expression of peptidylarginine deiminase-2 and-4, citrullinated proteins anti citrullinated protein antibodies in human gingiva. J Periodontal Res. 2013;48:252–261.

[27] Hensvold A-H, Reznisdottir G, Catrina A. From citrullination to specific immunity and disease in rheumatoid arthritis. Protein Deimin Human Health Dis. 2014;2:25–42.

[28] Abdukkah SN, Farmer EA, Spargo L, et al. Porphromonas gingivalis peptidylarginine deiminase substrate specificity. Anaerobe. 2013;23:102–108.

[29] Amara K, Steen J, Murray F, et al. Monoclonal IgG antibodies generated from joint derived B cells of RA patients have a strong bias towards citurllianted autantingen recognition. J Exp Med. 2013;3:445–455.

[30] Quirke AM, Lugli EB, Wegner N, et al. Heightened immune response to autocitrullinated Porphyromonas gingivalis peptidylarginine deiminase: a potential mechanism for breaching immunologic tolerance in rheumatoid arthritis. Ann Rheum Dis. 2014;73(1):263–269.

[31] Andrade F, Darrah E, Gucek M, et al. Autocitrullination of human peptidylarginine deiminase type 4 regulates protein citrullination during cell activation. Arthritis Rheum. 2010;62(6):1630–1640.

[32] Baka Z, György B, Géher P, et al. Citrullination under physiological and pathological conditions. Joint Bone Spine. 2012;79:431–436.

[33] Mikuls TR, Payne JB, Yu F, et al. Periodontitis and porphromonas gingivalis in patients with rheumatoid arthritis. Arthr Rheumatol. 2014;66(5):1090–1100.

[34] Wegner N, Lundberg K, Kinloch A, et al. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev. 2010;233:34–54.

[35] Arnson Y, Shoenfeld Y, Amita H. Effects of tabacco smoke on immunity, inflammation and autoimmunity. J Autoimmun. 2010;34:258–265.

[36] Lappin DF, Apatzidou D, Quirke AM, et al. Influence of periodontal disease, Porphyromonas gingivalis and cigarette smoking on systemic antic-citrullinated peptide antibody titres. J Clin Periodontol. 2013;40:907–915.

[37] Manivelavan D, Vijayasamundeeswari CK. Anti-cyclic citrullinated peptide antibody: an early diagnostic and prognostic biomarker of rheumatoid arthritis. J Clin Diagn Res. 2012;6(8):1393–1396.

[38] Gottenberg JE, Ravaud P, Cantagrel A, et al. Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the "Orencia and Rheumatoid Arthritis" registry. Ann Rheum Dis. 2012;7(11):1815–1819.

[39] Demoruelle MK, Parish MC, Derber LA, et al. Performance of anti-cyclic citrullinated peptide assazs differs in subjects at increased risk of rheumatoid arthritis and subjects with established disease. Arthritis Rheum. 2013;65:2243–2263.

[40] Gonzales SM, Payne JB, Yu E, et al. Alveolar bone loss is associated with circulating anti-citrullinated proteins antibody (ACPA) in patients with rheumatoid arthritis. J Periodontol. 2015;86(2):221–231.

[41] Ishi PE, Barros Bertolo M, Rossa Jr C, et al. Periodontal condition in patients with rheumatoid arthritis. Braz Oral Res. 2008;22(1):72–77.

[42] Pischon N, Pischon T, Kroger J, et al. Association among rheumatoid arthritis, oral hygiene, and periodontitis. J Periodontol. 2008;79:979–986.

[43] Dissick A, Redman RS, Jones M, et al. Association of periodontitis with rheumatoid arthritis: a pilot study. J Periodontol. 2010;81:223–230.

[44] Joseph R, Rajappan S, Nath SG, et al. Association between chronic periodontitis and rheumatoid arthritis: a hospital-based case-control study. Rheumatol Int. 2013;33(1): 103–109.

[45] Hendler A, Mulli TK, Hughes FJ, et al. Involvement of autoimmunity in the pathogenesis of aggressive periodontitis. J Dent Res. 2010;89:1389–1394.

[46] Seror R, David-Gall S, Bonnaure-Mallet M, et al. Association of anti-Porphromonas gingivalis antibody titers with nonsmoking status in early rheumatoid arthritis: results from the prospective French cohort of patients with early rheumatoid arthritis. Arthr Rheumatol. 2015;67(7):1729–1737.

[47] Kaur S, Bright R, Proudman SM, et al. Does periodontal treatment influence clinical and biochemical measures for rheumatoid arthritis? A systemic review and meta-analysis. Semin Arthr Rheum 2014;44:113–22.

[48] Potikuri D, Dannana KC, Kanchinadam S, et al. Periodontal disease is significantly higher in nonsmoking treatment-naïve rheumatoid arthritis patients: results from a case-control study. Ann Rheum Dis. 2012;71:1541–1544.

[49] Eriksson K, Nise L, Kats A, et al. Prevalence of periodontitis in patients with established rheumatoid arthritis: a Swedish population based case-control study. PLoS One. 2016;11(7):e0155956.

[50] Pinho Mde N, Oliveira RD, Novaes Jr AB, et al. Relationship between periodontitis and rheumatoid arthritis and the effect of non-surgical periodontal treatment. Braz Dent J. 2009;20:355–364.

[51] Bryrkoglu B, Buduneli N, Aksu K, et al. Periodontal therapy in chronic periodontitis lowers gingival crevicular fluid interleukin-1beta and DAS 28 in rheumatoid arthritis patients. Rheumatol Int. 2013;33:2607–2616.

[52] Moutsopoulos NM, Kling HM, Angelov N, et al. Porphromonas gingivalis promotes Th 17 inducing pathways in chronic periodontitis. J Autoimmun. 2012;39:294–303.

[53] Monsarrat P, Vergnes JN, Cantagrel A, et al. Effect of periodontal treatment on the clinical parameters of patients with rheumatoid arthritis: study protocol of the randomized, controlled ESPERA trial. Trials. 2013;14:253(1–9).

[54] Ortis P, Bissada NF, Paloma L, et al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. J Periodontal. 2009;80:535–540.

[55] Okada M, Kobayashi T, Ito S, et al. Periodontal treatment decreases levels of antibodies to porphryromonas gingivalis and citrulline in patients with rheumatoid arthritis and periodontics. J Periodontol. 2013;84(12):e74–e84.

[56] Erciyas K, Sezer U, Ustün K, et al. Effects of periodontal therapy on disease activity and systemic inflammation in rheumatoid arthritis patients. Oral Dis. 2013;19:394–400.

[57] Fisher BA, Cartwright AJ, Quirke AM, et al. Smoking, Porphyromonas gingivalis and the immune response to citrullinated autoantigens before the clinical onset of rheumatoid arthritis in a Southern European nested case-control study. BMC Musculoskelet Disord. 2015;16:331(1–11).