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Does a biological link exist between periodontitis and rheumatoid arthritis?

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Abstract

Periodontitis or Periodontal disease (PD) and Rheumatoid arthritis (RA) are two the most common chronic inflammatory diseases. Periodontitis is a biofilm associated destructive inflammatory disease of the periodontium caused by specific microorganisms. Rheumatoid arthritis is an autoimmune condition and is identified by elevated serum autoantibody titre directed against citrullinated peptides or rheumatoid factor. Periodontitis may involve some elements of autoimmunity. Recent studies have established that PD and RA show a common pathway and could be closely associated through a common dysregulation and dysfunction in inflammatory mechanism. The enzyme peptidyl arginine deiminase (PAD), expressed by *Porphyromonas gingivalis* (*P. gingivalis*) is responsible for the enzymatic deimination of arginine residuals to citrulline resulting in protein citrullination and its increased accumulation in RA. Citrullination by PAD may act as a putative biologic link between PD and RA. Association of Human leukocytic antigen-DR4 antigen has been established both with RA and PD. Several interleukins and inflammatory mediators (ILs) and Nuclear factor kappa beta ligand are linked to these common chronic inflammatory diseases. Antibodies directed against heat shock protein (hsp 70 ab) of *P. gingivalis*, *P. melanogenicus* and *P. intermedia* are raised in PD as well as RA. Both the conditions share many pathological and immunological similarities. Bacterial infection, genetic susceptibility, altered immune reaction and inflammatory mediators considered responsible for RA are also associated with PD. So it is plausible that a biological link may exist between PD and RA. Therapies aimed at modifying the expression and effect of inflammatory mediators and effector molecules such as matrix metalloproteinases, proinflammatory cytokines and autoantibodies of structural proteins may probably reduce the severity of both RA and PD.

Key words: Periodontal disease; Rheumatoid arthritis; Citrullinated peptidase; *Porphyromonas gingivalis*; Inflammatory marker; Inflammation and autoantibody

Core tip: Periodontal disease (PD) and Rheumatoid arthritis (RA) share many pathological and immunological similarities. Recent studies have established significant association between the two. Bacterial infection, genetic susceptibility, altered immune reaction and inflammatory mediators considered responsible for RA are also associated with PD. So it is plausible that a biological link may exist between PD and RA. Therapies aimed at reduction of inflammatory mediators and effector molecules can probably reduce the severity of both RA and PD.

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INTRODUCTION

Periodontal disease (PD) is an immuno inflammatory disease of the periodontium which comprises of both hard and soft tissues like gingiva, periodontal ligament, cementum and alveolar bone. It results from a complex interaction between gram negative organisms, their byproducts and the response of the host[1-4]. The resulting gingival inflammation leads to destruction of both the soft and hard tissues supporting the tooth[5]. The prevalence is said to be as high as 80% to 90%[6].

For periodontal tissues in a healthy state, a steady equilibrium exists between tissue destruction and repair. Periodontal destruction is initiated and progressed by specific periodontal microorganisms that colonize in plaque biofilm. Host microbial interaction determines the extent and severity of periodontal disease[7-9]. A large number of different species of bacteria can be identified in the dental plaque[10] but only a few of them are implicated in chronic periodontitis[11,12]. To prevent exacerbated reactions and destruction of host tissues, an appropriate tolerance mechanism is required by the host to recognize and identify nonpathogenic and pathogenic bacteria[13]. Pattern recognition receptors and microbe associated molecular patterns have a very significant role in periodontal inflammation and adaptive immune response[13,14].

The equilibrium established between anti-inflammatory and proinflammatory cytokines (IL-1α, IL-1β, TNF-α, IL-6[15], IL-7, IL-11, IL-17A, IL-17F, IFN-γ, IL-4, IL-10, IL-13, IL-16, IFN-α, TGF-β[16,17]) is responsible for the net inflammatory response. Increased levels of IL-1β, IL-12, IL-6, IL-17, TNF-α, and IFN-γ are reported in gingival tissues of chronic destructive periodontitis[18,19]. In periodontitis both Th1 (IFN-γ, IL-2, TNF-α) and Th2 (IL-4, IL-5, IL-6, IL-13) type cytokines are observed[20]. There is supporting evidence for the role of IL-17 and Th17 cells in periodontal disease[21]. IL-17 induces IL-6 and IL-8 secretion by gingival fibroblasts and also upregulates MMP - Matrix Metalloproteinases (MMP-1) and MMP-3 in these cells[22,23]. IL-17 also induces IL-1β and TNF-α secretion from macrophages and gingival epithelial cells[22,23]. Inflammatory cytokines are produced as a result of activation of toll like receptors of oral epithelial cells by the lipopolysaccharide of the gram negative periodontal pathogens[24]. Recently it has been reported that pathogenesis of many systemic diseases are associated with these inflammatory mediators. The pathways bridging periodontal infection and systemic health include transient bacteremia via metastatic infection, injury and inflammation resulting from immunological response induced by periodontal pathogens[25].

Recent studies have demonstrated that chronic periodontitis acts as a risk factor for systemic diseases like diabetes mellitus, cardiovascular disease, adverse pregnancy outcomes, rheumatoid arthritis etc[26-28].

Rheumatoid arthritis (RA) is a chronic inflammatory disease of articular joint with unknown etiology marked by a symmetric, peripheral polyarthritis and often results in joint damage and physical disability. The pathogenic hallmark of RA is synovial inflammation and proliferation, focal bone erosion and thinning of articular cartilage. Articular cartilage is an avascular tissue composed of a specialized matrix of collagen, proteoglycans and other proteins. Chondrocytes contribute to the unique cellular component. Cartilage is a highly responsive tissue that reacts to inflammatory mediators and mechanical factors, which in turn alters the balance between cartilage anabolism and catabolism. The structural damage to the mineralized cartilage and subchondral bone is mediated by osteoclasts[29].

Worldwide prevalence of RA, an autoimmune condition is approximately 1%[30]. It is diagnosed as chronic inflammatory polyarthritis when five or more joints are affected[29]. On close observation, a number of similarities seem to exist between the supporting periodontal structures and articular joint (Table 1).

SIMILARITIES BETWEEN RA AND PD

Periodontitis is a destructive chronic inflammatory disease of the periodontium caused by biofilm associated specific microorganisms[31-33]. Rheumatoid arthritis is an autoimmune condition and is characterized by elevated serum autoantibody titre directed against citrullinated peptides or rheumatoid factor (RF)[34,35]. Autoantibodies such as RF and anti-citrullinated protein/peptide antibody (ACPA) may be found in the sera of RA patients long before clinical onset of disease[27]. Periodontitis may also involve some elements of autoimmunity[36]. Autoantibodies and specific T cells against host molecules, such as type 1 collagen, have been detected in periodontal disease[23]. Recent studies have established statistically significant association between PD and RA[37-41]. The likelihood of PD among patients with RA is high. Also a higher prevalence of RA has been reported among patients with moderate to severe PD[41]. Joseph R. reported more periodontal destruction in RA group, pointing to a positive association between these diseases[42]. When comparing patients with RA and those with PD, many similarities have been reported in terms of serum cytokine and gene expression profiles, increased levels of serum matrix metalloproteinases, reactive oxygen species, lipid mediators, and neutrophil associated enzymes[5,43-46]. It has further been proposed that polymorphisms relating to genes encoding inflammatory cytokines might confer susceptibility to RA and PD[47-49]. Table 2 depicts some similarities observed in the pathogenesis of RA and PD.

Role of Porphyromonas gingivalis and immune response

Periodontal pathogens like *Porphyromonas gingivalis* (*P. gingivalis*) can invade the blood vessels and endothelial cells and lead to persistent bacteremia. It has the ability to in-

Table 1 Similarities between periodontal structures and articular joint

Supporting periodontal structures	Articular joint
Periodontal structures comprise of cementum, alveolar bone, periodontal ligament, gingival crevicular fluid and gingiva	Articular joints comprise of articular cartilage, bone, ligaments, synovial cavity, synovial fluid, and synovial capsule
Cementum is an avascular tissue	Articular cartilage is an avascular tissue
Periodontal ligament is a thin connective tissue that surrounds the root connecting it to the alveolar bone	Synovial tissue is a thin layer of connective tissue. It consists primarily of two cell types-type A synoviocytes (macrophage derived) and type B synoviocyte (fibroblast derived)
Periodontal ligament is collagenous and consists of epithelial rests of malassez, fibroblasts, osteoblasts and ground substances (hyaluronic acid and proteoglycans-fibronectin and laminin)	Synovial fibroblasts are the most abundant and produce the structural components of the joints including collagen, fibronectin and laminin
Gingival crevicular fluid is an infiltrate of blood	Synovial fluid is an infiltrate of blood

Table 2 Similarities in pathogenesis periodontal disease and rheumatoid arthritis

PD	RA
Chronic immunoinflammatory disease	Chronic immunoinflammatory disease
Periodontal pathogen is the main etiological agent with some element of autoimmunity	Bacteria/peptide as an adjunct antigen in autoantibody production
HLA-DR antigen association	HLA-DR antigen association
Inflammatory infiltrate mainly consists of B cells, plasma cells, PMN, T cell, dendritic cell, and macrophages	Inflammatory infiltrate consists of T cell, B cell, plasma cell, dendritic cell, mast cell, macrophages, and few granulocytes
Increases level of IL-1, TNF-α, PGE2, MMPs, NF-κB, RANK/RANKL/OPG, osteoclast activation	Increases level of IL-1, TNF-α, PGE2, MMPs NF-κβ, RANK/RANKL/OPG, osteoclast activation
Th1, ↑ ed Th2 and Th 17	Th1 = Th2 and Th 17
Role of nitric oxide	Role of nitric oxide
Genetic and environmental influences	Genetic and environmental influences
Bacterial DNA of anaerobes and high antibody titres against heat shock protein of *P.gingivalis*, *P. Melanogenicus* and *P. Intermedia*[95]	Bacterial DNA of anaerobes and high antibody titres against heat shock protein of *P. gingivalis*, *P. Melanogenicus* and *P. Intermedia*[95]

PD: Periodontal disease; RA: Rheumatoid arthritis; IL: Inflammatory mediator; MMPs: Matrix metalloproteinases; HLA: Human leukocytic antigen; HLA-DR: Human leucocyte antigen- D related; RANK: Receptor activator of nuclear factor kappa-β; RANKL: Receptor activator of nuclear factor kappa-β ligand; OPG: Osteoprotegerin; *P. gingivalis*: *Porphyromonas Gingivalis*; *P. intermedia*: *Prevotella intermedia*; *P. melaninogenicus*: *Prevotella melaninogenicus*; TNF: Tumor necrosis factor; NF-κB: Nuclear factor - kappa β; IL: Interleukin; PGE2: Prostaglandin E2.

vade primary chondrocytes of knee joints. As a result, cell cycle progression gets delayed, ultimately leading to accelerated apoptosis of these chondrocytes[50]. The virulence of *P. gingivalis* is mainly associated with its trypsin like proteolytic activity and ability to produce arginine and lysine -specific cysteine endopeptidase like gingipain R and gingipain K respectively[51]. Gingipain aids in evasion of host defense, tissue destruction and infection[52,53]. It leads to activation of MMPs (1, 3 and 9) and degradation of host proteins (laminin, fibronectin and collagen)[54]. Being the only identified bacterium with expression of peptidyl arginine deiminase (PAD), *P. gingivalis* and PAD represent a notable pathogenic element of RA[55-58]. PAD catalyses the deimination of arginine residuals to citrulline, a form of post-translational protein modification[59] which leads to an irreversible translation of arginine to citrulline[56,59]. However one important difference is that PAD expressed by *P. gingivalis* and human PAD are not exactly homologous[56,59]. It has been reported that in RA there is an increased citrullination of structure proteins[60]. This probably accounts for the fact that *P. gingivalis* titre significantly correlates with ACPA titre in RA patients[56,61-65].

GENETIC PROFILE IN PD AND RA

The most potent disease risk gene in RA and PD is the genome on the human leukocytic antigen (HLA) region[66]. HLA-DR4 antigen is associated with both RA and PD. This genetic association between these chronic inflammatory conditions also points to the biologic link between them[65,67-69]. Hitchon and colleagues have reported an association between *P. gingivalis* and the presence of ACPA in a population with predominant RA-predisposing HLA-DRB1 alleles. This gene-environment interaction may contribute to the breaking up of self-tolerance to citrullinated proteins. It could also amplify autoimmune reactions which could predispose to RA[70].

MARKERS OF INFLAMMATION IN PD AND RA

The synovial fluid of RA patients is rich in proinflammatory cytokines and many interleukins, (IL-1, IL-6, IL-8, IL-15, and IL-17) as well as NF-κB ligand (RANKL) which can be linked with RA[71,72]. Similar profile of inflammatory mediators has been identified in chronic periodontitis[35,73,74]. Elevated serum levels of TNF-α is associated with both these chronic inflammatory diseases[74,75]. Lipopolysaccharides and other bacterial byproducts stimulate the release of TNF-α and it upregulates the release of prostaglandin E2 (PGE2) and MMPs that stimulate osteoclast activation. These inflammatory processes ultimately lead to bone resorption in both RA and PD[76].

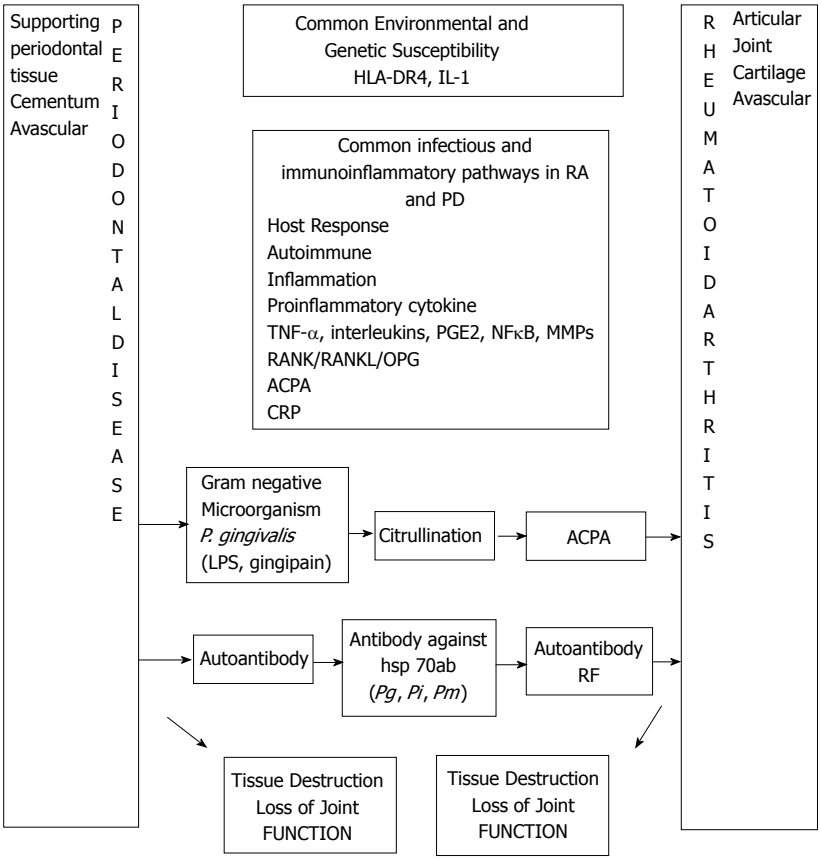

Figure 1 Hypothetical model of biological link between rheumatoid arthritis and periodontal disease. ACPA: Anti-citrullinated protein/peptide antibody; CRP: C reative protein; HLA: Human leukocyte antigen; hsp: Heat shock protein; LPS: Lipopolysaccharide, MMPs: Matrix metalloprotienases; NFκB: Nuclear factor kappa β; OPG: Osteoprotegerin; PD: Periodontal disease; PGE2: Prostaglandin E2; RANK: Receptor activator of nuclear factor kappa β; RANKL: Receptor activator of nuclear factor kappa β ligand; RA: Rheumatoid arthritis; RF: Rheumatoid factor; TNF-α: Tumor necrosis factor alpha; ACPA: Anti-citrullinated protein; RF: Rheumatoid factor; *P. gingivalis*: *Porphyromonas gingivalis*; IL: Interleukin.

EFFECTS OF THERAPY FOR RHEUMATOID ARTHRITIS ON PERIODONTAL DISEASE AND THERAPY FOR PERIODONTAL DISEASE ON RHEUMATOID ARTHRITIS

It has been suggested that treatment of periodontitis in patient with RA improved their response to RA therapy[77-80]. Treatment of RA with disease modifying antirheumatic drugs (DMARDS) improves their periodontal condition due to its host modulatory effect, thus masking the gingival inflammation and actual periodontal destruction[81-83]. Similarly, reduction in the systemic inflammation by the additional effect of periodontal therapy may also have been masked by DMARDs[35]. Al-Katma *et al*[84] assessed the role of scaling and root planning (SRP) on RA and demonstrated that there was an improvement in RA scores in the test group as compared to the control group. Advances in treatment of RA have identified novel therapeutic targets such as anticytokine therapy. Anti-TNF-α therapy used to control RA may also be beneficial in the management of periodontitis[85-88]. Ortiz *et al*[77] assessed the additional effect of non-surgical periodontal therapy (NSPT) in RA patients under anti-TNF-α therapy and reported that regardless of the medications, supportive periodontal therapy had a positive result on the clinical features of RA. In the absence of periodontal treatment anti-TNF-α therapy alone had no relevant outcome on the periodontal condition[77].

DOES A BIOLOGIC LINK EXIST BETWEEN PERIODONTAL DISEASE AND RHEUMATOID ARTHRITIS?

First of all, PD and RA share many pathological and immunological similarities. A cyclic nature of disease activity is seen in both RA and PD. There is evidence to suggest that PD could act as a potential risk factor for RA[24,89,90]. Similarly, RA subjects have significantly increased clinical attachment loss (CAL)[19-21]. Increased levels of antibodies to periodontopathic bacteria are reported to have been identified in sera and synovial tissues of patients with RA[63,70,81,91]. Correlation of serum level IgG antibodies to *P. gingivalis* with anticyclic citrullinated peptide indicates that serum protein citrullination via peptidyl arginine deiminase of *P. gingivalis* drives RA responses[63,70]. Citrullination by PAD may act as a biologically plausible mechanistic link between PD and RA. Furthermore the presence of RA might predispose individuals to PD[92,93]. Clinical trials suggest that treatment of PD has a significant effect on RA severity and vice versa[84,94].

Second, it is suspected that *IL-1* gene polymorphism affects the cytokine protein in RA and PD. HLA DR4 antigen is associated with both the conditions which points to the biological link between the two[67].

Third, it is reported that antibodies against heat shock protein (hsp 70 ab) of *P. gingivalis, P. melanogenicus and P. intermedia* are elevated not only in supporting periodontal tissues but also in synovial tissue of articular joints of RA patients[91,95].

Fourth point, Both RA and PD have shown raised titres of IL-10, IL-1α , IL-1β, MMPs, TNF-α ,LT-α and low titres of IL-1α and IL-6[45]. A common inflammatory marker dysfunction seems to be associated with both the articular joint and supporting periodontal tissue.

Bacterial infection, genetic susceptibility, altered immune reaction and inflammatory mediators considered responsible for RA are also associated with PD. So it is plausible that a biological link may exist between PD and RA (Figure 1).

EVIDENCES LINKING PD AND RA

Several studies have revealed that the prevalence of PD was high in patients with RA[40,42] and that PD severity was greater in RA patients[45]. Mercado *et al*[39] (2001) demonstrated a relation between RA and severity of periodontitis in a case control clinical study. Pischon *et al*[40] (2009) in a cross sectional clinical study showed significantly more CAL in RA subjects as compared to non-RA subjects. They have concluded that oral hygiene may account for this association to some extent. Kobayashi *et al*[49] (2007) reported that IL-1 and FCγR gene polymorphism have potential risk for RA and periodontitis.

Martinez-Martinez *et al*[96] (2009) in a case series clinical study on subjects with refractory RA and periodontitis found that *P. intermedia, P. gingivalis,* and *T. denticola* were the most predominant gram negative bacteria identified in synovial fluid, which substantiates the concept of anti-CCP and citrullinated structure protein. Dissick *et al*[41] (2010) in a case control study demonstrated that RA+ patients have more moderate to severe periodontitis. They have reported that females and smokers are at more risk in the RA+/periodontitis complex

Okada *et al*[81] (2011) demonstrated that corticosteroids, anti-rheumatic drugs, NSAIDs and TNF-α antagonists therapy improved the clinical features of periodontitis in RA patients. Presence of anti-PG IgG antibodies in RA+ patients may influence the serum RF level and periodontal health status[81]. Mayer *et al*[83] (2009) in a case control study concluded that TNF-α levels correlated with overall CAL and that inhibition of proinflammatory cytokines may account for the reduction of periodontal parameters. In another case control study, Ribeiro *et al*[94] (2005) evaluated the role of NSPT on RA status and found that RF decreased after periodontal intervention. The effects of NSPT in subjects with and without RA was studied by Pinho Mde *et al*[97] (2009) and they stated that that the relation between RA and periodontal disease activity is unclear. The effect of NSPT on RA patients under anti-TNF-α was studied by Ortiz *et al*[77] (2009) who inferred that NSPT had a positive effect on the clinical parameters of RA. Okada *et al*[98] in (2013) suggested that periodontal treatment decreases the levels of antibodies to *P. gingivalis* and citrulline in patients with RA and Periodontitis. They concluded that these observations may reflect the role of *P. gingivalis* in the protein citrullination which is related to the pathogenesis of RA[98]. Kaur *et al*[78] (2014) in a systematic review and meta analysis reported that non surgical periodontal therapy could lead to improvement in clinical and biochemical disease activity in RA.

Quirke *et al*[99] in 2013 reported that *P. gingivalis* is seemingly distinctive among periodontal pathogens in having PPAD (*P. gingivalis* peptidylarginine deiminase) with potential to evoke autoimmune response. They opined that the peptidyl citrulline specific immune response to PPAD might break tolerance in RA and could be a target for therapy[99]. Agnihotri *et al*[100] in (2014) reviewed the link between RA and PD in the elderly and inferred that thorough understanding of the link between the two chronic inflammatory diseases might be beneficial in rendering better health care protection and betterment of the life style of aged individuals.

CONCLUSION

The relationship between RA and PD can be attributed to common dysfunction and dysregulation in inflammatory mechanisms. Apparently, the common factors are bacterial lipopolysaccharides and inflammatory mediators. Development of specific autoantibodies by citrullination of protein by *P. gingivalis* may be the connecting link between RA and PD. Therapies aimed at suppression of inflammatory mediators and effector molecules such as MMP, proinflammatory cytokines and autoantibodies of structural proteins may probably reduce the severity of both RA and PD.

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