# The Association between Chronic Periodontitis and Rheumatoid Arthritis-A Review

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***Abstract-*** Chronic periodontitis although a common disorder in adults, is found associated with a number of systemic conditions like diabetes mellitus, atherosclerosis, coronary heart disease-CHD and certain chronic inflammatory disorders including rheumatoid arthritis. Rheumatoid Arthritis (RA) and Chronic Periodontitis-CP share certain common features like both being chronic inflammatory disease associated with bone loss and destruction of the soft tissue surrounding the bone ultimately leading to loss of function. Etiopathologically both are initiated by some pathogens like bacteria and believe to be further mediated by host immune-inflammatory dysregulation. Elevated levels of pro-inflammatory cytokines leading to bone resorption is reported in both conditions. Resolving periodontal infection seems to have positive effect on the treatment of RA. Both respond to certain drugs like NSAIDS and tetracyclines. This article reviews the association of CP and RA and how the successful treatment of periodontal condition affects the prognosis of the other disease.

***Index Terms***- chronic periodontitis, rheumatoid arthritis, association

## I. INTRODUCTION

Periodontal disease usually refers to the inflammatory disorder affecting the hard and soft tissues surrounding teeth[1]. Causative factor of this disorder is the plaque with its bacterial biofilm. The inflammatory process set upon due to this biofilm may result in destruction of the periodontal ligament and the alveolar bone[2]. If the condition persists or progress, the attachment apparatus of the tooth is affected that the tooth becomes loosened in the socket and ultimately exfoliate [1].

Chronic periodontitis is found to be associated with many systematic diseases like atherosclerosis, coronary heart disease, myocardial infarction and stroke[3,4]. Periodontitis has been reported as an independent risk factor for atherosclerosis including stroke [5] and coronary heart disease[6,7,8],and diabetes[9]. Chronic conditions of altered connective tissue metabolism, hormone imbalance and altered immune function[10] also seem to be associated with chronic periodontitis. Among these, the association of rheumatoid arthritis with chronic periodontitis has been widely studied and researched. Both are chronic inflammatory diseases with loss of bone and destruction of soft tissues surrounding the bone [11] Increased incidence of periodontitis in RA patients than healthy subjects has been observed in some studies [1,12]. RA and CP might share some similarity in their etio-pathogenesis[13].Their pathological resemblances are osseous erosion, periosteal soft tissue damage, similar humoral and cellular immune response and common immunogenetic mechanism[13].

## II. PATHOGENESIS OF CHRONIC PERIODONTITIS

Bacterial infection in periodontitis:

Infection of the periodontium is caused by some periodontopathogens like P.gingivalis, A.actinomycetemcombitans, P.intermedia B.forsythus P.melaninogenica, P.intermedia and E.notatum. Though bacteria are commonly implicated in the pathogenesis of periodontitis, some viruses were also found in periodontal pockets. Herpes virus was often believed to be responsible for the exacerbation of perodontitis. However the contribution of herpes virus to periodontitis remains controversial[14]. Other viruses reported to be present in the periodontal pocket are Papilloma virus, HIV, Human T lymphotropic virus type 1, Hepatitis B and C, Ebstein-Barr virus and Cytomegalovirus[15].

A.actinomycetamcombitans, T. forsythia, P.gingivalis are strongly associated with severity and progression of periodontal disease, causing failure of periodontal therapy. Other bacteria like P. Intermedia, P.nigrescens, C.rectus , Parvimonas micra, F. nucleatum, E. bacterium nodatum are moderately associated with the periodontal disease. Such infection is usually succeeded by chronic inflammation of the periodontal tissues mediated by T cells and other inflammatory mediators. Thus the sub-gingival bacterial bio-film initially establishes an infection which triggers the host inflammatory-immune response to cause bone loss and destruction of soft tissues surrounding the tooth [16]. Though bacterial products promote tissue destruction, inflammation is the major contributor for the degeneration of periodontal tissues in CP [15].

Virulence factors

Bacteria evade host immunity through production of extra-cellular capsule, modulation of host response by binding to serum components and invasion of gingival epithelial surface[15]. Virulence factors are

- those promoting colonization of microbes
- Toxins and enzymes
- Mechanisms protecting bacteria from the host

LPS-Lipopolysaccharide are present in the outer membrane of gram negative bacteria elicits strong immune reaction in the host. LPS is recognised in the host by the TLR- toll-like receptors. Once LPS has been recognised by the TLR this event is followed by a series of cellular events due to activation of CD14/TLR4/MD2 complex triggering increased production of inflammatory mediators and differentiation of immune cells for the effective immune response against the pathogens.

Lipo-teichoic acid-LTA of gram positive bacteria also elicits immune reactions in the host but not as effective as LPS. TLR2 recognise LTA.

Enzymes like proteases produced by bacteria may cause destruction of structural proteins like collagen, elastin and fibro-nectin of the periodontium leading to further bacterial invasion. Proteases also disrupts host response. P gingivalis produces two types of cysteine proteases, the arginine and lysine specific-gingipains, which are implicated in periodontal pathogenesis. Gingipains can alter immune-inflammatory response aiding in tissue breakdown. They increase IL-6, and IL8 secretion by monocytes [15].

Fimbriae of some bacteria especially P.gingivalis plays an important role in periodontal pathogenesis. Pili of A. actinomycetamcombitans also play an important role in the pathogenesis[15].

Inflammatory mediators:

Host derived inflammatory mediators such as cytokines, prostaglandins and matrix metalloproteinases - MMPs are believed to be responsible for the progression of CP [17,18,19]. and also in the pathogenesis of RA. MMPs are proteolytic in nature causing lysis of extra-cellular matrix like collagen, elastin and gelatin. Thus they mediate connective tissue destruction and induce differentiation and activity of osteoclast to destroy bone [20,21]. TNF α promote bone resorption by upregulation of inducible nitric oxide synthetase (iNOS) and production of nitric oxide [22], alteration of RANKL/OPG - ratio (RANKL-receptor activated nuclear kappa b ligand, OPG-osteoprotegerin) there by stimulating osteoclastic activity [19] and induce apoptosis of fibroblast thus impairing repair[15]. High titres of IL-10,IL 1α, and TNF α were found in CP patients.[23]

## III. Risk factors

Smoking is a major risk factor influencing the extent and severity of periodontitis. Though the mechanism by which smoking influences periodontitis is unknown [15], it seems to impair the immune response by reducing chemotaxis, phagocytic activity of PMNs and reducing the levels of IgA and IgG. Smokers are at greater risk for periodontitis compared to non-smokers. They experience more bone loss, furcation involvement and increased pocket depth than non-smokers. Alteration in the sub-gingival microflora and less bleeding on probing has been observed. Healing following periodontal therapy is compromised in smokers than non-smokers [24,25]

Emotional stress influence the extent and severity of CP, probably by affecting the immune function of the individual.

## IV. Pathogenesis of Rheumatoid Arthritis

RA is a chronic systemic inflammatory disease mainly affecting the joints causing non-suppurative proliferative synovitis progressing to destruction of articular cartilage and resorption of bone[26].

The exact etiology of RA is unknown. It is believed 'RA is triggered by exposure of an immnunogenetically susceptible host to an arthritogenic microbial antigen' [26]. The arthritogenic microbe cause an acute arthritis followed by a continuing autoimmune reaction mediated by T cells. This is also accompanied with local release of inflammatory mediators and lytic cytokines, resulting in destruction of the joint. Genetic predisposition is major determinant of susceptibility to RA especially HLA-DR4 or DR1 or both. Therefore factors involved in the casuation of RA are 1. An arthritogenic antigen 2. Autoimmune reaction with synovial membrane and 3.mediators of the joint damage. 4.Genetic susceptibility [26].

Initiation of RA could be due to some microbial agent, acting as arthritogenic antigen. EB virus is believed to be an important etiological agent in RA followed by retrovirus, parvovirus, mycobacteria, borrelia and mycoplasma[26]. However recently, the periodontopathogenic bacteria P.gingivalis by its expression of the enzyme peptidyl arginine deaminase-PAD and other mechanism could contribute to development of RA also[27]. P.gingivalis has been found to invade human chondrocytes of knee joints and increase the apoptosis of chondrocytes. They also believed to delay cell cycle progression [27,28].

Following infection of the synovium, T cells mainly CD4 cells appear at the inflammatory site with the release of IL-1, TNF α, INF γ. CD4 cells activate monocyte-macrophage and promote release of monokines. They also activate B cell production in the affected joints. IgM autoantibodies to Fc portion of autologous IgG (Rheumatoid factor RF) are found in RA. However RF is not present in all cases. Activated CD4 cells, B cells and macrophage secrete IL-1,IL-2,IL-3,IL4,IL-6, IFN γ, TNF α, and TNF β. Neutrophils produce proteases and elasteases. TNFα or IL 1 induce release of collagenases causing resorption of bone and cartilage [26].

## V. The possible association of chronic periodontitis and rheumatoid arthritis

Many possible mechanisms have been proposed to explain the association of periodontitis and rheumatoid arthritis. Oral infections contributing to the pathogenesis of RA is one such theory [29]. RA is believed to be caused by arthritogenic microbial antigen.

Increased levels of immunoglobulins G and A (IgG and IgA) against some periodontopathogenic bacteria were found in both the serum and synovium of patients with RA. This fact may suggest that these bacteria and their antibodies act as a possible aetiopathogenic mechanism in RA [29].

The highly pathogenic bacteria P. gingivalis is one of the key pathogen in periodontitis and is believed to be the only known bacterium that could express the enzyme PAD. This enzyme is also believed to be an important pathogenic factor for RA. During inflammation the enzyme PAD converts arginine to citrulline. This post-translational modification alters the bio-

chemical and antigenic nature of the protein/peptide structure [30] resulting in generation of auto-immunity to these citrullinated peptides. In RA antibodies to citrullinated protein such as keratin, filagrin, fibrin, vimentin, fibrinogen as well as antibodies to anticyclic citrullinated peptide-CCP have been reported as specific for the disease. This may ultimately result in the development of RA[31].

P gingivalis also seem to disrupt the integrity of epithelium, affect endothelial cells and impact transcription and synthesis of proteins[28]. Thus they may have direct access to systemic circulation. The bacteria also found to affect the human chondrocytes of knee joint and promote their apoptosis[28]. Thus infection by p. gingivalis may cause RA or exacerbate the condition[29].

Bacteria has been mainly implicated in the pathogenesis of CP. Onset or progression of CP by viruses and other microorganism remains controversial. RA is believed to be caused by viruses like EBV[26]. However recent reports of isolation of periodontopathogens from synovium and serum of RA patients show some inclining towards a common pathogenic organism in both disorders.

Elevated levels of cytokines are seen in chronic periodontitis and rheumatoid arthritis also. Such elevated levels of inflammatory mediators are found not only at the inflammatory sites i.e diseased periodontium and synovium, but also reflected in the systemic circulation Increased levels of cytokines like as IL-1,IL 6 and TNF α has been observed in the serum of CP, RA and Juvenile Idiopathic Arthritis patients [17,18,32]. These pro-inflammatory cytokines like IL-1,6, TNF α are seen to be responsible for bone resorption[26,33].

HLA-DR4 gene susceptibility is seen in CP as with RA. Katz et al in 1987 conducted a study to confirm the association between HLA-DR4 and RPP- rapidly progressing periodontitis. In this study, higher frequency (42%) of DRB1 sub-type was observed in RPP patients than the control group[34]. This DRB1 sub-types are also observed in inflammatory diseases like RA [29].

Hence all the four factors- genetic susceptibility, bacterial infection, altered host immune reaction and inflammatory mediators, which are considered responsible for RA [26] is also associated with Periodontitis. The clinical comorbidity of the two disease possibly relies on a common etiology and pathology[29]

CP and RA share certain common risk factors. These risk factors may influence the 'sub-steps of pathogenesis' contributing to varied clinical manifestation of both conditions [27]. Individual risk factors include age, gender and body mass. Exogenic risk factors are nutrition, socio-economic condition and stress. Habits like cigarette smoking and alcohol consumption, and presence of systemic diseases also influence the pathogenesis.[35,36]

Smoking is one of the well-known risk factor for RA and CP. Though smoking is believed to affect the function of immune cells, the mechanism by which smoking affects both these conditions remain unknown. Smoking increases the susceptibility of RA, only in individuals with auto-antibody positive RA with presence of ACPA- anti-citrullinated protein/peptide antibody. Risk for RA is associated with smoking, shared epitope allele and presence of ACPA [37]. However the clear association between smoking, CP, RA, and presence of ACPA have not been established yet[37].

Mercado F et al in a study found 4 times increase in RA in periodontitis patients than patients not referred for periodontal treatment [1]. The authors concluded that moderate to severe periodontitis might be a risk factor for RA and vice-versa.

Golub et al have proposed a hypothetic two-hit model for the periodontitis- systemic disease correlation following the pattern of a two-hit model for ADRS proposed by Carney et al and Steinberg et al [38,39,19]. The two hit model of Steinberg et al proposed that 'two simultaneous hits' by systemic and local factors trigger the disease progression. Steinberg et al experimented in Yorkshire pigs inducing ADRS for the two-hit model. ADRS is a fatal lung disease associated with VILI - ventilator induced lung injury, mediated by inflammatory mediators (cytokines, prostonoids and Nitric Oxide) and effector molecules like MMPs. The 'first hit' was the inducing of VILI in Yorkshire pigs and 'second hit' was the injection of endotoxin. This induced polymorphonuclear degranulation and thereby caused irreversible lung disease.

Based on this, Golub et al in their two-hit model have proposed that systemic diseases not just exacerbate periodontitis but they co-induce the disease. The 2nd hit for periodontitis is believed to be caused by the elevated serum levels of inflammatory mediators like cytokines, prostonoids, C-Reactive Proteins and MMPs caused by systemic conditions like rheumatoid arthritis. These elevated levels of circulating cytokines are thought to initiate cytokine/prostaglandin/MMP/RANKL cascade locally in the periodontium, especially when coinduced by bacterial factors such as lipopolysachharide LPS- the 1st hit. The increased levels of effector molecules like MMPs and other bone tissue destructive proteinases might cause alveolar bone loss. Thus their hypothetic two-hit model suggests that periodontitis and systemic disease like RA not just coexist but could co-induce each other [19]. Scher et al have examined sub-gingival microbiota by prosequencing in new-onet RA patients. P.gingivalis was more frequently observed in new-onset RA patients compared to established or healthy controls. The authors correlate the higher prevalence of severe periodontitis in those untreated RA patients to the presence of p.gingivalis in those cases [40].

A cross-sectional clinical, serological and microbiological study was conducted by Smith et al, to ascertain whether the association between periodontitis and RA is dependent on the presence of cultivable p.gingivalis in sub-gingival plaque [41]. In their study they also observed the increased prevalence of periodontitis in patients with RA as with similar prevalence studies conducted before. In this study they also noticed anti-p.gingivalis titres were higher in RA patients with severe periodontitis compared with non-RA patients. But the severity of RA was not associated with cultivable p.gingivalis in established RA patients[41].

In 2011, Cantley MD et al in an experimental study performed in mice found that pre-existing periodontitis exacerbated collagen antibody induced arthritis. Perodontitis was induced by P.gingivalis[42]. Similarly Queiroz-Junior CM et al in 2012 conducted an experimental study in mice, in which AIA-antigen induced arthritis was found to exacerbate A.actinomycetamcombitans –induced periodontitis[43]. Thus

presence of one condition may exacerbate the other disease. The relationship between RA and CP could be bidirectional [42].Exacerbation of RA signs in patients with CP and incidence of increased CP in patients with RA also have been reported [43]. The common immunogenetic-inflammatory resemblance of the two disorders is believed to be responsible for this.

Modi DK et al reviewed the association of rheumatoid arthritis and periodontitis. Clinical correlation, biological links and common therapeutic modalities of both the disorders had been correlated in the review[23].Under biologic links the authors have correlated

- PAD expressed by the periodontogenic bacteria p.gingivalis, which has been considered as risk factor for RA,
- presence of antibodies against heat shock proteins of P.melaninogenica and P.intermedia in periodontium as well as in synovium of RA patients, and
- raised titres of inflammatory mediators like cytokines in both disorders. Among the cytokines, IL-1, IL 6 and TNF α are commonly found elevated in both conditions.

RA and CP respond to Bisphosponates, tetracycline analogues and NSAIDS [23].

Bisphosponates are drugs that inhibit osteoclasts. Some studies have shown that new-generation bisphosphonates, like zoledronic acid reduce bony erosion in RA patients[44]. Bisphosphonates were reported to inhibit alveolar bone loss and increase bone mass [45] in CP patients.

Both RA and CP are characterised by the presence of elevated MMPs. MMPs are proteases causing destruction of connective tissues. Tetracyclines are broad spectrum antibiotics reducing the activity of MMPs by chelating the cofactors of MMPs [46,47], thereby preventing their protein degradation action. tetacycline has been reported useful in treating RA [48] and CP patients [49] by their anti-MMP activity.

Both RA and CP are chronic inflammatory diseases responding to NSAIDS though the mechanism of action varies. In CP prostaglandin E2 has been found in increased levels. Some in-vivo studies have shown that prostaglandin E2 mediate bone resorption. NSAIDS acts by inhibition of cycloxygenase and thereby preventing prostaglandin formation. Some animal and human studies have shown that inhibition of cyclooxygenase by NSAIDS has therapeutic efficacy in periodontitis because of prevention of formation of prostaglandins. The mechanism of action of NSAIDS in RA is independent of its cycloxygenase inhibitory effect i.e NSAIDS inhibit the activation and function of neutrophils. NSAIDS also prevent TNF release from monocytes and non-killer cells. These effects could aid in their efficacy in the treatment of RA [23]

Emerging therapies common to both RA and CP include Ornidazole [50] chemically modified tetracyclines, Osteoprotegrin and conjugated linoleic acid

Monsarrat et al conducted a randomized trial –ESPERA i.e. experimental study of periodontitis and rheumatoid arthritis to see if the treatment of periodontitis could improve the outcomes of RA [51] .Subjects with both RA and CP were recruited. CP patients were treated with non-surgical periodontal therapy consisting of full mouth supra-gingival, sub-gingival scaling and root planing followed by systemic antibiotic therapy, local antiseptics and oral hygiene instructions. Though their small sample was small, they have noticed considerable improvement in their Disease Activity Score. Such improvement had been reported by two other trials conducted by Al-Katma et al and Oritz P et al. [52,53]

## VI. Conclusion

Considering the common etiopathological, altered immune-inflammatory system of the host causing elevated levels of inflammatory mediators, presence of antibodies against periodontopathogens in the serum and synovium of RA patients, expression of PAD and citrullination of peptides by P.gingivalis causing auto-antibodies against these altered peptide structures, increased severity of PD in RA patients and vice-versa and certain common treatment modalities suggests that there could be association between these two diseases. Successful treatment of one problem could positively affect the outcome of the other disorder when they occur simultaneously. Thus diagnosis of periodontal disease and its treatment modalities, in future could become part of the ‘diagnostic and treatment kit’ for RA.

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