IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861. Volume 12, Issue 5 (Nov.- Dec. 2013), PP 01-04
www.iosrjournals.org

Periodontal disease and Rheumatoid Arthritis – A Review

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Abstract: *Periodontal medicine defines a rapidly emerging branch of Periodontology focusing on establishing a strong relationship between periodontal health and systemic health. Periodontitis and rheumatoid arthritis are widely prevalent diseases and are characterized by tissue destruction due to chronic inflammation. Several prospective clinical trials have shown that individuals with rheumatoid arthritis are more likely to experience moderate to severe periodontal disease compared to their healthy counterparts. There are growing evidences that the two diseases share many pathological features. This review elaborates the common pathologic mechanisms of these two chronic conditions.*
Keywords:*Bacteria, cytokines, inflammation, periodontitis, rheumatoid arthritis.*

I. Introduction:

Periodontitis is one of the most common periodontal disease of infectious origin known in humans with a prevalence of 10-60% in adults depending on diagnostic criteria [1]. In periodontitis, the clinical findings of bone resorption and the clinical attachment loss around the tooth are a result of inflammatory mediated alterations to the bone remodeling balance. The inflammatory infiltrate present between the plaque biofilm, bone and connective tissues regulate the host immune response to the bacteria. The host produces proteases and substances that degrade the extracellular matrix, and lead to the resorption of alveolar bone, resulting in irreversible loss of tissue attachment.

Rheumatoid arthritis is a systemic autoimmune disease characterized by progressive joint destruction, and a variety of systemic manifestations resulting from chronic inflammation. It affects approximately 1% of the adult population [2]. Rheumatiod arthritis is characterized by inflammation of the synovial membrane, leading to the invasion of synovial tissue into the adjacent cartilage matrix with degradation of articular cartilage and bone. Matrix metalloproteinases, cathepsins, and osteoclast activation significantly contribute to bone erosion [3].

Periodontitis and rheumatoid arthritis are arguably the most prevalent chronic inflammatory diseases in humans and associated with significant morbidities. Periodontitis and rheumatoid arthritis share similar clinical and pathogenic charecteristics, with an imbalance between proinflammatory and anti-inflammatory cytokines, which is thought to be responsible for the tissue damage. Both the conditions are associated with the destruction of bone, mediated by inflammatory cytokines such as interleukin-1, tumor necrosis factor and prostaglandin E2 [4].

II. The Role of History:

2.1 Periodontal disease: Natural history studies of periodontal disease in humans indicate the presence of three distinct subpopulations: [5]

1) No progression of periodontal disease, in which around 10% of the population manifest very little or no disease which is of no particular consequence to the dentition.

2) Moderate progression, affecting around 80% of the population
and representing a very slowly progressing form of disease that generally can be easily managed via routine therapies.

3) Rapid progression, affecting approximately 8% of individuals whereby extensive periodontal destruction occurs which can be very difficult to control.

From the natural history studies of RA and periodontitis, it has been observed that certain RA and periodontitis populations are characterized by a particular type of patient who will experience disease progression irrespective of any treatment provided.

2.2.Rheumatoid arthritis: Here three types of disease manifestation can be observed in RA populations:

1) Self-limited: in these cases individuals originally presenting RA have no evidence of disease 3 to 5 years later [6].

2) Easily controlled: the disease is relatively easily controlled with only nonsteroidalanti-inflammatory drugs (NSAIDs) [7].

3) Progressive: these patients generally require second-line drugs, which often still do not fully control the disease [8,9].

III. Role of etiologic Factors:

3.1Periodontitis:Periodontitis, has a specific inflammatory response to specific periodontal pathogens residing in the subgingival biofilm and there is considerable variability in terms of clinical manifestation and disease progression rates. This variability can be due to differences in composition of the subgingival microbial flora, as well as factors that modify the host response to the microbial challenge. It should be understood that, although bacteria are necessary for disease initiation, they are not sufficient to cause disease progression unlessthere is an associated inflammatory response within a susceptible host [10].

3.2Rheumatoid arthritis:Although the cause of RA is unknown, it has been recognized that many different arthritogenic stimuli activate inflammatory responses in immunogenetically susceptible hosts [11]. Thus, studies have focused on exogenous infectious agents, endogenoussubstances, such as connective tissue proteins (e.g., collagens and proteoglycans), and alteredimmunoglobulins as the causative factors. Different animal modelsdemonstrate that arthritis can develop secondarily to severaldifferent stimuli and through several different effector pathways. If such observations are also applicableto human RA, it is anticipated that differenttypes of infections as well as other environmental exposures with capacity to induce excessive proinflammatorycytokines in genetically susceptible individuals may all potentially contribute to disease.

IV. The Role of Bacteria:

There are a number of common links between microorganisms that can induce RA in a genetically susceptible host and the recognized periodontal pathogens. Nonetheless, RA is still not largely recognized as a disease resulting solely from bacterial challenge. On the other hand, technological and conceptual advances have permitted the identification of bacteria or groups of bacteria associated with specific periodontal diseases [12]. Close inspection of the virulence factors of periodontal pathogens would suggest that such a response could be feasible. Until this day, no infectious agents have been identified as the cause of RA in humans. Indeed, current information does not support the concept that a single antigen is responsible for synovial inflammation. It is possible that there is no single primary cause of RA and that different mechanisms may independently lead to synovial inflammation in susceptible individuals. The main focus of attention is directed not towards causality but rather associations between two chronic inflammatory conditions that may have common underlying pathogenic mechanisms.

V. Role of Immunogenetics:

5.1 Periodontitis: It has been reported that more than 50% of the variance in several features of chronic periodontitis can be explained by genetic factors. Many of these variables relate to severity of periodontal destruction, and other inflammatory responses are attributed partly to the amount and type of cytokines that individuals produce [13]. While theHLA-DR phenotype is not particularly strong for periodontitis, there is a report indicating that it is animportant component of the genetic susceptibility tosome forms of this disease. In addition, polymorphismsin the interleukin-1β (IL-1β) gene cluster havebeen shown to have a significant correlation withsome forms of periodontitis in certain populations [14].

5.2 Rheumatoid Arthritis: Studies on monozygotic and dizygotic twins have shown that RA has several features indicative of a complex genetic disease including genetic variance, incomplete penetrance, and multiple gene involvement [15]For RA, the strongest genetic associations are found within the HLA genes.Using DNA sequencing and molecular-based typing, it has been demonstrated that the disease-conferring portion of the D region isconfined to a short sequence within the third hypervariableregion of HLA-DRB1 gene which includes the amino acid positions 67 through 74 [16]. The HLA genes and gender constitute about 30% of the genetic risk in RA, while other genetic factors such as cytokine genes, germline genes, and T-cell receptors also account for some of the genetic predispositionto RA.

VI. Effector Mechanisms of Tissue Destruction:

There is almost universal acceptance that a variety of cytokines and matrix metalloproteinases (MMPs) are upregulated and intimately involved in the pathogenesis of both periodontitis and RA; many of these effector molecules appear to be common to both diseases. The task now is to identify the specific cytokines, their concentrations, the cells they affect in vivo, the stages in which they are active, and the role and concentrationsof their inhibitors.Cytokines can be classified into functional groups based on the cells of origin, and all major types have been identified and located in inflamedsynovial and periodontal tissues.

Periodontitis has very similar cytokine profiles toRA [17,18], consisting of persistent high levels of proinflammatorycytokines, including IL-1βand tumor necrosis factor-alpha (TNF-a), and low levels of cytokines which suppress the immunoinflammatory response such as IL-10 and transforming growth factor-β (TGF-β). These cytokines, together with low levels of tissue inhibitors of metalloproteinases(TIMPs) and high levels of MMPs and prostaglandin E2 (PGE2), are associated with the active stages of periodontitis. The destruction of soft and hard tissues seen inRA is also the result of not only a large number of cytokines but also the sustained presence of other effector molecules released by resident and migrating cells. Together, these soluble mediators of inflammation are able to induce degradation of collagen and proteoglycans either through direct or indirect means. Production of the arachidonic acid metabolite PGE2 as well as the release of neutrophil-associated enzymes, such as neutrophil elastase and β-glucuronidase, together with the secretion of matrix metalloproteinases by macrophages and synoviocytes, all contribute significantlyto the pathogenesis of RA.

VII. Associated Studies Between Periodontitisand Rheumatoid Arthritis:

Several studies on the association between RA have been published. Most studies have used the criteria for RA defined by the American College of Rheumatology [19]., and the criteria for periodontitis defined by the American Association of Periodontology. Odds ratios that subjects with RA have more frequently and with more severe periodontitis varied between OR: 2.2:1 [20] and OR: 8.1:1 [21], Periodontal disease severity (OR: 2.1:1) was ranked as number three as a predictivefactor for RA with female gender (OR: 7:1). Other studies have not assessed the likelihood of an association but rather defined shared etiological factors or host response mechanisms between RA and periodontitis.

One of the problems in assessing proinflammatory factors in RA and periodontitis is that some studiesrepresent convenience studies where subjects at the time of assessment were treated with a variety of common medication against RA symptoms. Thus, the lack of higher TNF-α and CRP serum levels in subjects with both RA and periodontitis may be explained by the impact of anti-inflammatory routine RA medications [22-25].

In one well-controlled clinical case-control study [26] study including hospitalized RA patients, analyzing the frequency of different oral bacterial DNA species in periodontal pocket samples, sera, and synovial fluids of patients with RA and controls, the authors identified variable bacterial DNA concentration of bacteria with an oral origin in synovial fluids and in serum from the patients with RA. In one case series [27] including 19 subjects remaining after screening of 500 subjects with RA refractory subjects not responding to disease modifying antirheumatic drugs (DMARDS)and periodontitis assessed the presence of pathogens (by PCR method) associated with periodontitis. The study identified that, in bacterial samples from knee joints, such bacteria were found in 100% of samples including one or several species. Among the most prevalent species were Prevotellaintermedia, Treponemadenticola, and P. gingivalis.Aggregatibacteractinomycetemcomitanswas the least commonly found microorganism.

VIII. Similarities in Pathogenesis and Treatment:

Currently, the mainstream ‘‘first-line’’ modes of treatmentfor RA remain the NSAIDs such as aspirin, naproxen, diclofenac, and ibuprofen. Their mechanism of action through the inhibition of cyclooxygenase (COX) synthesis produces both analgesic and antipyretic properties. While these medications are effective in reducing the pain symptoms in RA, they do not significantly alter its course [28].

The use of NSAIDs for management of periodontal disease has been studied over the past 20 years [29].While the results appear promising, the widespread clinical use of these medications to alter the courseof periodontitis has not been universal.With the discovery of two COX enzymes responsible for PGE2 production, designated COX-1 (constitutively expressed) and COX-2 (inducible), a variety of COX-2 inhibitors have been studied for their potential to stop or slow down bone resorption. One of the first COX-2 inhibitors developed, tenidap, has been shown to inhibit not only cyclooxygenase and PGE2 production but also IL-1, IL-6, and TNF-α production. COX-2 inhibitors have not been thoroughly studied for their potential to modify bone resorptionin periodontitis. In contrast to the NSAIDS, which do not significantly alter the course of RA, a newer family of medications designated disease-modifying anti-rheumatic drugs (DMARDs) has been developed. To be classified as a DMARD, the medication must demonstrate an ability to change the course of RA for at least 1 year as evidenced by sustained improvement in function,decreased synovitis, and prevention of further joint damage [30]. The use of DMARDs for the management of periodontitis has been restricted largely due to the toxicity issues.

Another emerging area of potential for host modulation in periodontitis and rheumatoid arthritis is controlof the MMPs that are important mediators of connective tissue breakdown in both hard and soft tissues [31].

Many of these biologic agents, which target specific molecular events associated with acute and chronic inflammation, have significant potential to alter clinical outcomes for both RA and periodontal disease. With the emerging understanding that RA and periodontitis are multifactorial diseases, combination therapies

that target multiple disease outcomes are also emerging. However, until an etiologic factor can be found for RA, host modification remains the mainstay of treatment.

IX. Conclusion:

We conclude that there are some evidences for the relationship between the presence of periodontitis and the development of RA. The existence of an inflammatory systemic disease may promote periodontitis in both its emergence and progress. Periodontal pathogens have direct systemic action to the blood circulation, and so treatment with antibiotics in patients with RA can be effective. The current challenge to clinicians is the development of treatment regimens that suppress underlying RA, disease activity, inhibit endothelial dysfunction and effective control of periodontal disease progression with adjunctive therapies. For clinical studies, it is necessary to create a network of cooperation with Rheumatologist and Periodontists.

References:

[1]. Papapanau PN. Periodontal disease: Epidemiology. *Ann Periodontal* 1996;1:1-36.
[2]. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. *Autoinnun Rev* 2005;*4*:130-6.
[3]. Ciancio S, Ashley R. Safety and efficacy of sub-antimicrobial dose of doxycycline therapy in patients with adult periodontitis. *Adv Dent Res* 1998;12:27-31.
[4]. Cochran D. Inflammation and bone loss in periodontal disease. *Journal of Periodontology*. 2008;*79*:1569-76.
[5]. Hirschfeld L, Wasserman B. A long-term survey of tooth loss in 600 treated periodontal patients. *J Periodontol* 1978;*49*:225-237.
[6]. O'Sullivan JB, Cathcart ES. The prevalence of rheumatoid arthritis. Follow up evaluation of the effect of criteria on rates in Sudbury, Massachusetts. *Ann Intern Med* 1972*;76*:573-577.
[7]. Pincus T, Marcum SB, Callahan LF. Long term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. *J Rheumatol* 1992*;19*:1885-1894.
[8]. Pincus T, Marcum SB, Callahan LF, et al. Long term drug therapy for rheumatoid arthritis in seven rheumalology private practices: I. Non-steroidal anti-inflammatory drugs. *J Rheumatol* 1992*;19*:1874-1884.
[9]. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: A 14-year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990;*17*:994-1002.
[10]. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: Summary of developments, clinical implications and future directions. *Periodontol 2000* 1997;*14*:216-248.
[11]. Grassi W, De Angelis R, et al. the clinical features of rheumatoid arthritis. *European Journal of Radiology*. 1998;*27(suppl 1):*S18-24.
[12]. Zambon JJ. Periodontal diseases: Microbial factors. *Ann Periodontol* 1996*; 1*:879-925.
[13]. Savli GE, Brown CE, Fujihashi K, et al. Inflammatory mediators of the terminal dentition in adult and early onset periodontitis. *J Periodontal Res* 1998; *33*:212-225.
[14]. Kornman KS, Crane A, Wang H-Y, et, al. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J ClinPeriodontol* 1997; *24:*72-77.
[15]. Kurosaka M, Ziff M. Immunoelectron microscopic study of the distribution of T-cell subsets in rheumatoid synovium. *J Exp Med* 1983; *158*:1191-1210.
[16]. Nepom GT, Nepom BS. Prediction of susceptibility to rheumatoid arthritis by human leukocyte antigen genotype. *Rheum Dis Clin Am* 1992; *18*:785-792.
[17]. Snyderman R, McCarty GA. Analogous mechanisms of tissue destruction in rheumatoid arthritis and periodontal disease. In: Genco RJ, Mergenhagen SE, esd. Host-Parasite Interaction in Periodontal Diseases. Washington, DC: *American Society for Microbiology*; 1982:354-362.
[18]. Arend WP, Dayer JM. Cytokines and cytokine inhibitors or antagonists in rheumatoid arthritis. *Arthritis Rheum* 1990; *33*:305-315.
[19]. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; *31*:315-24.
[20]. Mercado RB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. *J Periodontol* 2001; *72*:779-87.
[21]. Pischon N, Pischon T, Kroger J, Gulmez E, Kleber BM, Bernimoulin JP, et al. Association between rheumatoid arthritis, oral hygiene and periodontitis. *J Periodontol* 2008; *79*:979-86.
[22]. Nilsson M, Kopp S. Gingivitis and periodontitis are related to repeated high levels of circulating tumor necrosis factor-alpha in patient with rheumatoid arthritis. *J. Periodontol* 2008; *79*:1689-96.
[23]. Biyikoglu B, Buduneli N, Kardesler L, Aksu K, Pitkala M, Sorsa T. Gingival crevicular fluid MMP-8 and -13 and TIMP-1 levels in patients with rheumatoid arthritis and inflammatory periodontal disease. *J. Periodontol*2009; *80*:1307-14.
[24]. DissickA, Redman RS, Jones M, Rangan BV, Reimold A, Griffiths GR, et al. association of periodontitis with rheumatoid arthritis: a pilot study. *J. Periodontol* 2010; *81*:223-30.
[25]. Ziebolz D, Pabel SO, Lange K, Krohn-Grimberghe B, Hornecker E, Mausberg RF. Clinical periodontal and microbiologic parameter in patients with rheumatoid arthritis. *J. Periodontol* 2011; *82*:1424-2.
[26]. Moen K, Brun JG, Valen M, Skartveit L, Eribe EK, Olsen I, et al. Synovial inflammation in active rheumatoid arthritis an psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. *ClinExpRheumatol* 2006; *24*:656-63.
[27]. Martinez-Martinez RE, Abud-Mendoza C, Patino-Marin N, Rizo-Rodriguez JC, Little JW, Loyola-Rodriguez JP. Detection of periodontal bacteria DNA in serum and synovial fluid in refractory rheumatoid arthritis patients. *J ClinPeriodontol* 2009; *36*:1004-10.
[28]. Lipsky PE. Rheumatoid arthritis. In: Wilson JD, Braunwald E, Isselbacher KJ, et al., eds. Harrison's Principles of Internal Medicine, 12th ed. New York: McGraw-Hill; 1991:1437-1443.
[29]. Paquette DW, Williams RC. Modulation of host inflammatory mediators as a treatment strategy for periodontal diseases. *Periodontol 2000* 2000; *24*:239-252.
[30]. Paget S. Treatment. In: Klippel J, ed. Primer on the rheumatic disease. Atlanta: *Arthritis Foundation* 1997:168-174.
[31]. Golub LM, McNamara TF, D'Angelo G, Greenwald RA, Ramamurthy NS. A non-antibacterial chemically modified tetracycline inhibits mammalian collagenase activity. *J Dent Res* 1987; *66*:1310-1314.