Review Article

International Journal of Dental and Health Sciences
Volume 04,Issue 04

CO-RELATION BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS: A PERIODONTIST'S PERSPECTIVE

Anita Singh[1], Vaibhav Sheel[2] , Shalini Kaushal[3], Nand Lal[4]

[1]Post graduate student, Department of Periodontology, King george's medical university, Lucknow, India
[2]Senior Resident, Department of Periodontology, King george's medical university, Lucknow, India
[3]Professor Juniorgrade, Department of Periodontology, King george' s medical university, Lucknow, India
[4]Professor and Head of the Department, Department of Periodontology, King george' smedical university, Lucknow, India

ABSTRACT:

In this review, we explore the similarity between rheumatoid arthritis (RA) and periodontitis. We consider genetic and environmental risk factors associated with RA and periodontitis. The role of oral microorganisms and host immune response in pathogenesis of RA are explored. According to recent evidence both conditions manifest as a result of an imbalance between proinflammatory and anti-inflammatory cytokines. As a result, new treatment approaches are expected to come out for both diseases that inhibit of proinflammatory cytokines and destructive proteases. Furthermore, we discuss adjunctive host modulation therapy, originally developed for periodontitis (i.e., sub antimicrobial-dose doxycycline). Finally, we discuss the studies describing periodontal treatment effects on both RA disease activity measures and systemic inflammation and whether periodontal treatment can reduce the severity of RA or prevent its onset. The clinical implications of the current data indicate that patients with RA should be carefully screened for their periodontal status. Further studies with sufficient sample sizes are required to verify relationship between these two diseases.

Key-words: Rheumatoid arthritis, Periodontitis, Host immune response

INTRODUCTION

Rheumatoid arthritis (RA) is chronic inflammatory autoimmune disease characterized by persistent synovitis, systemic inflammation, production of autoantibodies, and bone destruction of joints and is associated with significant morbidity and functional disability. Prevalence of RA is 0.5- 1.0 % in the adult population and its occurrence is more in female than male (3:1). [1, 2]

Periodontal diseases are affecting the supporting tissues of teeth. The first step in the gum-disease process is gingivitis, which is inflammation of gingiva without bone loss. [3]

In susceptible individuals gingivitis can progress into periodontitis, as results of host immune-inflammatory response to the bacterial colonization of tooth surfaces. Periodontitis is an advanced and more serious stage of gum disease, which includes alveolar bone loss, ultimately leading to tooth loss and affecting about 35 to 50% of adults.[4] Periodontitis share some pathogenic features with RA; both are chronic inflammatory diseases with genetic and environmental influences and immunoregulatory imbalance, and both lead to destruction of connective and hard tissues.[5]

It has been reported that the frequency of RA is significantly higher in patients with periodontal disease than in subjects

*Corresponding Author Address: Dr. Vaibhav Sheel. E-mail: vaibhavsheelgupta@gmail.com

without periodontitis (3.95% versus 0.66%). While the etiology of these two diseases may differ, the underlying pathogenic mechanisms are remarkably similar. [6] This article reviews their clinical and biological interrelation and current therapeutic approaches emerging from these links.

INTERLINKS BETWEEN RHEUMATOID ARTHRITIS AND PERIODONTITIS-

Natural history

Periodontal disease. Three different categories can be seen in periodontal disease populations. [7]

(1) Little or no progression of periodontal disease: approximately 10% of the population manifest very little or no disease.

(2) moderate progression: around 80% of the population have slowly progressing type of disease which often can be easily managed by regular therapies; and

(3) rapid progression: rapid periodontal destruction occurs in approximately 8% of individuals which can be difficult to control.

Rheumatoid arthritis. Three types of disease appearance can also be seen in RA populations:

(1) Self-controlled: these types of patients have no confirmation of disease 3 to 5 years later [8];

(2) easily treatable: this form of disease is relatively easily controlled with only non steroidal anti-inflammatory drugs (NSAIDS) [9];

(3) progressive: these patients generally require second-line drugs, which often still do not fully control the disease.

Patients with progressive type of RA are at risk to develop severe forms of periodontal disease remains to be established.

Role of oral infections

It is now generally accepted that chronic periodontitis is initiated by the colonisation of dental plaque by gram – ve anaerobe bacteria, especially Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola.[10] The highly pathogenic oral bacteria can sustain a chronic bacteremia that may harm joints and endocardium .[11]

The hypothesis that oral infections play a role in RA pathogenesis may be supported by the detection of bacterial DNA of anaerobes and high antibody titers against these periopathogens in both the serum and the synovial fluid of RA patients in the early and later stages of the disease. [12] Recently, it was demonstrated that P. gingivalis is able to invade primary human chondrocytes and to induce cellular effects. As results of this invasion, P. gingivalis delayed cell cycle progression and increased cell apoptosis in these chondrocytes that were isolated from knee joints. [13]

P. gingivalis expresses lipopolysaccharide (LPS), fimbrae, and haemagglutins, which make the bacterium to colonise and invade periodontal pockets, and is hence known as the “master manipulator” of the host homeostatic system.[14] most virulent factor of P. gingivalis is extracellular cysteine proteases, referred to as gingipains.[15,16] Because its gingipains make it resistant to complement, P.gingivalis helps in activation of the complement pathway, which initiates and maintains the inflammatory reaction.[17] In addition, gingipains favour other pathogenic bacteria co-aggregating with P. gingivalis to persist in the gingiva by degrading antimicrobial peptides. Moreover, gingipains affect proinflammatory signalling pathways by cleavage and activation of the proteinase-activated receptor-2 (PAR-2) on human neutrophils. Down regulation of host immune response to bacterial infection consequently lead to connective tissue damage, including alveolar bone resorption. [18, 19]

Role of citrullination in RA development

It has been demonstrated that P. gingivalis expresses peptidyl arginine deiminase (PAD), an enzyme that mediates posttranslational conversion of arginine to citrulline. [20] Biochemical and antigen characteristics of arginine are changed due to posttranslational modification. [21]

The underlying mechanism - proteolytic cleavage and subsequent citrullination at carboxy-terminal arginine residues - differs from that of the human PAD enzymes, which citrullinate internal arginine residues in whole proteins most efficiently. Protein citrullination by P. gingivalis PAD (PPAD) has the potential to generate epitopes to which immunological intolerance develop, not merely due to the presence of foreign citrullinated proteins from the bacterium, but also through a foreign mode of proteolytic processing and post-translational modification of host antigens.[60]

In genetically susceptible individuals, loss of tolerance initiates the generation of autoantibodies against citrullinated proteins (accp) in the synovium. [22] Citrullinated fibrin and α-enolase are two of the physiological proteins that are targeted by anti-citrullinated protein antibodies in RA [59]. Autoantibodies to citrullinated fibrin are found in up to 66 % of patients with RA [58]. Autoantibodies to citrullinated α-enolase can be found in 40–60% of patients with RA [58]. However there are no known factors which trigger the breakdown of tolerance to citrullinated proteins. Up till now, tobacco utilization and the presence of certain alleles in the HLA-DRB1 locus with a common peptide-binding pattern, have been recognized as risk factors for developing autoantibodies to citrullinated protein[61], in particular α-enolase and vimentin [62], but do not describe the total risk.

Several studies have demonstrated that serum levels of anti-cyclic citrullinated peptide (accp) antibodies were higher in patients with RA than those in without RA, additionally, serum levels of antibodies to P. gingivalis, were partially correlated with those of accp antibodies in patients with RA. These observations suggest the possibility that citrullination of bacterial and host proteins through PPAD would drive autoimmune responses and the subsequent development of RA. [23]

Heat shock proteins

Heat shock proteins (hsps) defend the cell from stress. Furthermore, hereditary and acquired immunity against hsps are associated with the pathogenesis of RA.[24] Antibodies against heat shock proteins (hsp 70 ab) of P-melaninogenica and P-intermedia have been found to be increased in the periodontal tissue, synovial tissue and in serum of patients with rheumatoid arthritis.[25] However it has been shown that the hsp 70 expression is also induced with certain stress-stimulating factors, (for example, heat, trauma, endotoxins, and anti-inflammatory drugs) and pro inflammatory cytokines (TNF-α, IL-1, and IL-6). Therefore hsp in patients with RA are not specific to oral bacteria. [25]

Genetic factors

Disease risk gene in RA and periodontitis is leukocytic antigen (HLA) region of human genome. [27] RA and periodontitis both are associated with HLA-DR4 antigen . This genetic relationship between these chronic inflammatory diseases also points to the link between them. [26, 28, 29]

Hitchon and colleagues have reported an association between P. gingivalis and the presence of acpa in individuals with predominant RA predisposing HLA-DRB1 alleles. This gene-environment interaction may leads to loss of tolerance to citrullinated proteins. It could also initiate autoimmune reactions which could predispose to RA. [30]

Mutual exacerbation of inflammatory responses

A “two-hit” model for the link between periodontitis and systemic diseases, including RA, was proposed by Golub et al. [31] Two-hit model is the mutual exacerbation of inflammatory responses: in susceptible individuals periodontitis serves as the first hit, whereas an (unknown) arthritrogenic hit induces RA (second hit) that leads to mutual exacerbation of the inflammatory responses causes tissue breakdown in both the joint and the periodontium. [31]

Neutrophils indirectly mediate destructive effects by chemotactic recruitment of T-helper 17 (Th-17) cells. Th-17 cells selectively produce the proinflammatory cytokine interleukin-17 (IL-17), which is crucial for host defense against extracellular pathogens. Both at onset and in established RA, uncontrolled Th-17 activity has been involved in joint inflammation and bone breakdown in RA. The presence of IL-17 and Th-17 cells in human periodontitis

may be associated with disease severity, possibly after activation of innate immune cells by P. gingivalis. [32]

A similar profile of cytokines including IL-1, IL-6, IL-18 and TNF-α, has been seen in the pathogenesis of RA and periodontitis. Levels of IL-1β are increased in the synovial tissue macrophages and in the periodontal crevicular fluid in patients with rheumatoid arthritis and periodontitis, respectively. [33]

Polymorphism of the IL-1 gene affected the cytokine profile in patients of both periodontitis and rheumatoid arthritis. C-reactive protein (CRP) is secreted in response to cytokines, such as IL-6, and has been considered a common inflammatory marker for both diseases. [34]

Rheumatoid factor (RF)

The rheumatoid factor (RF) has been found in patients of both periodontitis and rheumatoid arthritis. [35] RF seropositive patients with periodontitis showed increased titers **of** IgG and IgM antibodies against oral microorganisms when compared with RF seronegative patients with periodontitis. [36] The RF of seropositive patients shows a cross-reaction with oral bacterial epitopes. [37] P. gingivalis proteinase is responsible for the epitope development in the RF-Fc region. The proteinases are consider as important virulence factors because they help in the growth of P. gingivalis and leads to the degradation of the host tissue.[38] Bonagura and colleagues[39] identified the lysine and arginine amino acid sequences for these Fc regions of the IgG molecule. P. Gingivalis involve in the RF production by decomposition of lysine and arginine in particular and the IgG3 CH2 and CH3 domains are processed by the P. gingivalis proteinase.[40] Studies have demonstrated that RF was detected in gingival and sub gingival plaque, saliva, and serum of patients with periodontitis.[36] Serum anti–P.gingivalis titers were significantly correlated with serum RF levels, suggestive of an association between serum antibody responses to P.gingivalis and RF concentration in RA.

Smoking

Smoking is a risk factor associated to RA susceptibility. Significantly, smoking contribute to disease susceptibility in autoantibody-positive RA patients . There is a clustering of RA risk associated with smoking, presence of shared epitope alleles and the presence of acpa.[42] Smoking is risk factors associated to periodontitis susceptibility .[41] Smoking contribute to periodontitis maybe through direct effects on P. gingivalis gene expression or through the actions of nicotine on inflammatory cytokine profiles and MMP-3 activity .[43] Hitchon and colleagues[41] have demonstrated a high prevalence of both smoking and poor oral hygiene in the study population on the basis of self-report questionnaire data; however, they could not define a clear relationship

between these risk factors and the presence of either RA or acpa.

Studies on the effects of treatment of rheumatoid arthritis on periodontitis and the effects of periodontal therapy on rheumatoid arthritis conditions

NSAIDS such as aspirin, naproxen, diclofenac, and ibuprofen are ‘‘First-line’’ medications in RA . Their mechanism of action through the inhibition of cyclooxygenase (cox). These medications are helpful in reducing the pain in RA without alteration in its course. [44] For treatment of periodontal disease NSAIDS has been studied over the past 20 years. [45-47] ‘‘Rebound’’ effect to baseline after termination of the NSAIDS is the problem with their use for the management of periodontitis.[48]

Evidence have demonstrated that COX-2 inhibitors can decrease or inhibit bone resorption. Tenidap, a COX2 inhibitor, has been demonstrated to inhibit cyclooxygenase, PGE2, IL-1, IL-6, and TNF-a production. However COX-2 inhibitors have not been considered for their potential to alter bone resorption in periodontitis.

A newer family of medications designated disease-modifying anti-rheumatic drugs (DMARDS) has been developed. [49]

Host modulatory effect of DMARDS improves periodontal conditions in RA patients, thus obscure the gingival inflammation and actual periodontal destruction.[50,51,52] Similarly, the improvement in periodontal conditions due to decrease in systemic inflammation after periodontal therapy may also have been obscure by DMARDS.[53] Treatment with DMARDS improved periodontal conditions, this favour the infectious link between periodontitis and RA.

Anti-TNF-α therapy used in treatment of RA may also be helpful in the management of periodontitis. Without periodontal treatment anti-TNF-α therapy alone had no benefit on the periodontal condition. [56]

Evidences shown that treatment of periodontitis in patient with RA improved their response to RA therapy.[56] Ortiz et al . demonstrated the additional effect of non-surgical periodontal therapy (NSPT) in RA patients under anti-TNF-α therapy and reported that in spite of of the medications, supportive periodontal therapy also decreases the signs and symptoms of RA.[34]

Systemically administered anti-collagenolytic sub antimicrobial dose of doxycycline(SDD) and locally delivered antibacterial doxycycline both as an adjunct to mechanical debridement may be useful in treating periodontitis as well as RA. Local and systemic host modulatory approach may be useful in treating RA and chronic periodontitis simultaneously because acpa are involved in the pathogenesis of RA. [54]

Supragingival scaling decreases serum levels of IgG to P. gingivalis HBP-35 and

citrulline in patients with RA. Elimination of periodontal pathogens by scaling and root planing might reduce exposure of the joints structures to bacteria, their toxins and subsequently lead to improved RA conditions. [34] Studies have demonstrated reduction in signs and symptoms of active rheumatoid arthritis as well as reduction in severity of RA as measured by disease activity score (DAS-28)after scaling and root planing in subjects with moderate to severe periodontal disease due to control of infection and inflammation .[57]

Non-surgical periodontal treatment may establish useful in reducing severity of RA as measured by ESR, CRP and TNF-α levels in serum in low or moderate to highly active RA patients with chronic periodontitis.[55

CONCLUSION:

Non surgical periodontal therapy leads to decrease in severity and symptom of active rheumatoid arthritis. Hence, rheumatoid arthritis patients should be evaluated for periodontitis and treated for the same in order to reduce its severity level.

REFERENCES:

1. Sacks JJ, Luo YH, Helmick CG. Prevalence of Specific Types of Arthritis And Other Rheumatic Conditions, In The Ambulatory Health Care System, In The United States. Arthritis Care Res. 2010; 62: 460-4.
2. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel Se. Is The Incidence Of Rheumatoid Arthritis Rising? Results From Olmsted County, Minnesota. Arthritis Rheum. 2010; 62: 1576-82.
3. Saini R: Periodontitis A True Infection. J Glob Infect Dis. 2009; 1:149-151.
4. Listgarten Ma: Bacteria And Periodontitis. J Can Dent Assoc .1996; 62:12-13.
5. B. T. Garib And S. S. Qaradaxi, “Temporomandibular Joint Problems And Periodontal Condition In Rheumatoid Arthritis Patients In Relation To Their Rheumatologic Status,” Journal Of Oral And Maxillofacial Surgery. 2011; 69:2971-2978
6. Mercado F, Marshall Ri, Klestov Ac, Bartold Pm. Is There A Relationship Between Rheumatoid Arthritis And Periodontal Disease? J Clin Periodontol. 2000; 27:267–272.
7. Hirschfeld L, Wasserman B. A Long-Term Survey Of Tooth Loss In 600 Treated Periodontal Patients. J Periodontol.1978; 49:225-237.
8. 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.
9. 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.
10. Socransky Ss, Haff Ajee Ad. Dental biofilms: difficult therapeutic targets. Periodontol 2000, 2002; 28:12-55.
11. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmstrom V, Feldmann

M, Venables Pj: Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev.2010; 233:34-54.

12. Moen K, Brun Jg, Valen M, Skartveit L, Eribe Ek, Olsen I, Jonsson R: Synovial infl ammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial dnas. Clin Exp Rheumatol. 2006; 24:656-663.
13. Pischon N, Roehner E, Hocke A, N'guessan P, Mueller Hc, Matziolis G, Kanitz V, Purucker P, Kleber Bm, Bernimoulin Jp, Burmester Gr, Buttgereit F, Detert J: Effcts of porphyromonas gingivalis on cell cycle progression and apoptosis of primary human chondrocytes. Ann Rheum Dis. 2008; 68:1902-1907.
14. Hajishengallis G, Liang S, Paynema, Hashima, Jotwani R, Eskan Ma, Et Al. Low-abundance biofilm species orchestrates inflammatory periodontal disease through the commensal microbiota and complement. Cell Host Microbe. 2011; 10:497–506.
15. Guo Y, Nguyen Ka, Potempa J. Dichotomy of gingipains action as virulence factors: from cleaving substrates with the precision of a surgeon's knife to a meat chopper-like brutal degradation of proteins. Periodontology 2000.2010; 54:15–44.
16. Krauss JL, Potempa J, Lambris Jd, Hajishengallis G. Complementary Tolls In The Periodontium: How periodontal bacteria modify complement and toll-like receptor responses to prevail in the host. Periodontology 2000. 2010; 52:141–62.
17. Potempa M, Potempa J. Protease-dependent mechanisms of complement evasion by bacterial pathogens. Biol Chem.2012;393:873–88.
18. Ford Pj, Gamonal J, Seymour Gj. Immunological differences and similarities between chronic periodontitis and aggressive periodontitis. Periodontology2000. 2010; 53:111–123.
19. Liu Yc, Lerner Uh, Teng Yt. Cytokine responses against periodontal infection: protective and destructive roles. Periodontology 2000. 2010; 52:163–206.
20. Mcgraw Wt, Potempa J, Farley D, Travis J: Purification, characterization, and sequence analysis of a potential virulence factor from porphyromonas gingivalis, peptidylarginine deiminase. Infect immune. 1999; 67:3248-3256.
21. Schellekens Ga, Visser H, De Jong Ba, Van Den Hoogen Fh, Hazes Jm, Breedveld Fc, Van Venrooij Wj: The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000; 43:155-163.
22. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmstrom V, Feldmann M, Venables Pj: Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev. 2010; 233:34-54.
23. Hitchon Ca, Chandad F, Ferucci Ed, Willemze A, Ioan-Facsinay A, Van Der Woude D, Markland J, Robinson D, Elias B, Newkirk M, Toes Rm, Huizinga Tw, El-Gabalawy Hs. Antibodies to porphyromonas gingivalis are associated with anticitrullinated protein antibodies

in patients with rheumatoid arthritis and their relatives. J Rheumatol. 2010;37:1105-1112.
24. Ragno S, Colston MR, Lowrie DB, Winrow VR, Blake DR, Tascon R. Protection of Rats from adjuvant arthritis by immunization with naked dna encoding for mycobacterial heat shock protein 65. Arthritis Rheum. 1997; 40:277-283.
25. Ogrendik M. Rheumatoid arthritis is linked to oral bacteria: etiological association. Mod Rheumatol. 2009; 19:453-456.
26. Mikuls Tr, Thiele Gm, Deane Kd, Payne Jb, O'dell Jr, Yu F, Sayles H, Weisman Mh, Gregersen Pk, Buckner Jh, Keating Rm, Derber La, Robinson Wh, Holers Vm, Norris Jm. Porphyromonas gingivalis and disease-related autoantibodies in individuals at increased risk of rheumatoid arthritis. Arthritis Rheum. 2012; 64: 3522-3530
27. Kinloch Aj, Alzabin S, Brintnell W, Wilson E, Barra L, Wegner N, Bell Da, Cairns E, Venables Pj. Immunization with porphyromonas gingivalis enolase induces autoimmunity To mammalian α-enolase and rthritis in DR4-IE-transgenic mice. Arthritis Rheum. 2011; 63: 3818-3823
28. Marotte H, Farge P, Gaudin P, Alexandre C, Mougin B, Miossec P. The association between periodontal disease and joint destruction in rheumatoid arthritis extends the link between the HLA-DR shared epitope and severity of bone destruction. Ann Rheum Dis. 2006; 65: 905-909
29. Kapitány A, Zilahi E, Szántó S, Szücs G, Szabó Z, Végvári A, Rass P, Sipka S, Szegedi G, Szekanecz Z. Association of rheumatoid arthritis with HLA-DR1 and HLA-DR4 in hungary. Ann N Y Acad Sci. 2005; 1051: 263-270
30. Hitchon Ca, Chandad F, Ferucci Ed, Willemze A, Ioan- Facsinay A, Van Der Woude D, Markland J, Robinson D, Elias B, Newkirk M, Toes Rm, Huizinga Tw, El-Gabalawy Hs. Antibodies to porphyromonas gingivalis are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. J Rheumatol. 2010; 37:1105-1112.
31. Jeffrey B. Payne, Lorne M. Golub, Geoffrey M. Thiele Et Al. The link between periodontitis and rheumatoid arthritis: A periodontist's perspective curr oral health rep. 2015; 2: 20–29.
32. Tesmer La, Lundy Sk, Sarkar S, Fox Da: Th-17 cells in human disease. Immunol Rev. 2008; 223:87-113.
33. Cardoso Cr, Garlet Gp, Crippa Ge, Rosa Al, Junior Wm, Rossi Ma, Silva Js: Evidence of the presence of T helper type 17 cells in chronic lesions of human periodontal disease. Oral Microbiol Immunol. 2009; 24:1-6.
34. Ortiz P, Bissada Nf, Palomo L, Et Al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. J Periodontol, 2009;80:535-540.
35. Rosenstein Ed, Greenwald Ra, Kushner Lj, Weissmann G: Hypothesis. The humoral immune response to oral bacteria provides a stimulus for the development of rheumatoid arthritis. Infl Ammation, 2004;28:311-318.

36. Mcgraw Wt, Potempa J, Farley D, Travis J. Purification, characterization, and sequence analysis of a potential virulence factor from porphyromonas gingivalis, peptidylarginine deiminase. Infect Immun, 1999; 67:3248-3256.
37. The J, Ebersole Jl: Rheumatoid factor from periodontitis patients crossreacts with epitopes on oral bacteria. Oral Dis, 1996; 253-262.
38. Bonagura Vr, Artandi Se, Davidson A, Randen I, Agostino N, Thompson K, Natvig Jb, Morrison Sl. Mapping studies reveal unique epitopes on igg recognized by rheumatoid arthritis-derived monoclonal rheumatoid factors. J Immunol, 1993; 151:3840-3852.
39. Potempa J, Banbula A, Travis J. Role of bacterial proteinases in matrix destruction and modulation of host responses. Periodontol 2000, 2000;24:153-192.
40. Martin T, Crouzier R, Weber Jc, Kipps Tj, Pasquali Jl. Structure-function studies on a polyreactive (natural) autoantibody. Polyreactivity is dependent on somatically generated sequences in the third complementaritydetermining region of the antibody heavy chain. J Immunol, 1994;152:5988-5996.
41. Hitchon Ca, Chandad F, Ferucci Ed, Willemze A, Ioan-Facsinay A, Van Der Woude D, Markland J, Robinson D, Elias B, Newkirk M, Toes Rm, Huizinga Tw, El-Gabalawy Hs. Antibodies to porphyromonas gingivalis are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. J Rheumatol, 2010; 37:1105-1112.
42. Lundstrom E, Kallberg H, Alfredsson L, Klareskog L, Padyukov L. Gene environment Interaction between the DRB1 shared epitope and smoking in the risk of anti-citrullinated protein antibody-positive rheumatoid arthritis: all alleles are important. Arthritis Rheum, 2009; 60:1597-1603.
43. De Heens Gl, Kikkert R, Aarden La, Van Der Velden U, Loos Bg. Effects of smoking on the ex vivo cytokine production in periodontitis. J Periodontal Res, 2009; 44:28-34.
44. Lipsky Pe. Wilson Jd, Braunwald E, Isselbacher Kj, Et Al. Harrison's principles of internal medicine, Rheumatoid Arthritis In: 1991:1437-1443.
45. Feldman Rs, Szeto B, Chauncey Hh, Goldhaber P. Non-steroidal anti-inflammatory drugs in the reduction of human alveolar bone loss. J Clin Periodontol, 1983;10:131-136.
46. Jeffcoat Mk, Page R, Reddy M, Et Al. Use of digital radiography to demonstrate the potential of naproxen as an adjunct in the treatment of rapidly progressive periodontitis. J Periodontal Res, 1991;26: 415-421.
47. Paquette Dw, Williams Rc. Modulation of host inflammatory mediators as a treatment strategy for periodontal diseases. Periodontol 2000, 2000;24:239- 252.
48. Williams Rc, Jeffcoat Mk, Howell Th, Et Al. Altering the progression of human alveolar bone loss with the non-steroidal anti-inflammatory drug flurbiprofen. J Periodontol, 1989;60:485-490.
49. Paget S. Treatment. In: Klippel J, Ed. Primer on the rheumatic diseases: Arthritis Foundation; 1997:168-174.

50. Okada M, Kobayashi T, Ito S, Yokoyama T, Komatsu Y, Abe A, Murasawa A, Yoshie H. Antibody responses to periodontopathic bacteria in relation to rheumatoid arthritis in japanese adults. J Periodontol, 2011; 82: 1433-1441
51. Han Jy, Reynolds Ma. Effect of anti-rheumatic agents on periodontal parameters and biomarkers of inflammation: A Systematic Review And Meta-Analysis. J Periodontal Implant Sci, 2012; 42: 3-12
52. Mayer Y, Balbir-Gurman A, Machtei Ee. Anti-tumor necrosis factor-alpha therapy and periodontal parameters in patients with rheumatoid arthritis. J Periodontol, 2009; 80: 1414-1420
53. Rutger Persson G. Rheumatoid arthritis and periodontitis-inflammatory and infectious connections. J Oral Microbiol, 2012; 4
54. Garrett S, Adams Df, Bogle G, Donly K, Drisko Ch, Hallmon Ww, Et Al. The effects of locally delivered controlled-release doxycycline or scaling and root planing on periodontal maintenance patients over 9 months. J Periodontol, 2000;71:22–30.
55. Erciyas K1, Sezer U, Ustün K, Pehlivan Y, Kisacik B, Senyurt Sz, Tarakçioğlu M, Onat Am. Effects of periodontal therapy on disease activity and systemic inflammation in rheumatoid arthritis patients. Oral Dis, 2013;19:394-400
56. Kiarash O, Bissada Nf, Arauz-Dutari J, Et Al. Impact of anti-tnf therapy on periodontitis in rheumatoid arthritis patients. J Dent Res,2007 Abst. #2506.
57. Ribeiro J, Lea˜O A, Novaes Ab. Periodontal infection as a possible severity factor for rheumatoid arthritis. J Clin Periodontol, 2005;32:412-416.
58. Snir O, Widhe M, von Spee C, Lindberg J, Padyukov L, Lundberg K, et al. Multiple antibody reactivities to citrullinated antigens in sera from patients with rheumatoid arthritis: association with HLA-DRB1 alleles. Ann. Rheum. Dis 2009;68(5):736–743.
59. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmström V, Feldmann M, et al. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunological Reviews 2010;233(1):34–54.
60. Lundberg K, Kinloch A, Fisher BA, Wegner N, Wait R, Charles P. et al. Antibodies to citrullinated alpha-enolase peptide 1 are specific for rheumatoid arthritis and cross-react with bacterial enolase. Arthritis Rheum 2008;58(10):3009–3019.
61. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54(1):38–46.
62. Mahdi H, Fisher BA, Kallberg H, Plant D, Malmstrom V, Ronnelid J, et al. Specific interaction between genotype, smoking and autoimmunity to citrullinated alpha-enolase in the etiology of rheumatoid arthritis. Nat Genet 2009;41(12):1319–1324.