REVIEW ARTICLE

Rheumatoid arthritis and periodontitis: Biological links and the emergence of dual purpose therapies

Depinder Kaur Modi, Vipinder Singh Chopra, Usha Bhau[1]

Department of Pharmacology, Government Medical College, [1]Sarwal Hospital Jammu, J & K Health Services, Jammu 180 001, India

Received : 17-02-07
Review completed : 25-04-08
Accepted : 23-06-08
PubMed ID : 19336867
DOI: 10.4103/0970-9290.49070

ABSTRACT

Rheumatoid arthritis and periodontitis are widely prevalent diseases and are characterized by tissue destruction due to chronic inflammation. Recently, there is growing evidence that the two diseases share many pathological features. This article reviews their clinical and biological links. However, there are only a limited number of studies in this area, which prevent us from offering clear evidence.

Key words: Biological linkages, periodontitis, rheumatoid arthritis

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.[1] Rheumatoid arthritis is characterized by the inflammation of the synovial membrane, leading to an invasion of the synovial tissue into the adjacent cartilage matrix with degradation of the articular cartilage and bone. Though the pathophysiological mechanism of cartilage and bone destruction in rheumatoid arthritis is not exactly understood, it is known that matrix metalloproteinases, cathepsins, and osteoclast activation significantly contribute to bone erosion.[2,3] A number of cytokines like TNF-α, IL-1, and macrophage colony stimulating factor (MCSF) are also involved.[4]

Periodontal disease is one of the most common chronic disorders of infectious origin known in humans with a prevalence of 10–60% in adults depending on the diagnostic criteria.[5] It includes gingivitis (an inflammatory condition of soft tissues surrounding the tooth) and periodontitis (a bacterial infection of the periodontium). Periodontitis is the most common type of periodontal disease. Most patients of periodontitis respond to bacterial invaders by mobilizing their defensive cells and releasing cytokines like interleukin-1β, tumor necrosis factor-α, and interleukin-6, which ultimately causes tissue destruction by stimulating the production of collagenolytic enzymes like matrix metalloproteinases.[6] Recently, there has been growing evidence suggesting an association between periodontitis and the increased risk of systemic diseases such as atherosclerosis, diabetes mellitus, adverse pregnancy outcome, and rheumatoid arthritis. Periodontitis and rheumatoid arthritis share many pathological aspects and immunological findings. This article reviews their clinical and biological interrelation and current therapeutic approaches emerging from these links [Table 1].

Address for correspondence:
Dr. Depinder Kaur Modi,
E-mail: drdeepinder@rediffmail.com

CLINICAL INTERELATION

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.[7] On the other hand, some studies have reported a high incidence of rheumatoid arthritis in patients with periodontitis.[8] This clinical association between the two diseases might be due to a common underlying pathobiology of periodontitis and rheumatoid arthritis [Figure 1].

BIOLOGICAL LINKS

1. Periodontitis is caused by periodontopathic bacteria like actinobacillus actinomycetemcomitans, porphyromonas gingivalis, bacteroides forsythus, prevotella melaninogenica, prevotella intermedia, and eubacterium nodatum.[9] Pathogen-specific immunoglobin (IgG and IgA) levels against some of these bacteria have been found to be raised in the synovial fluid of patients with rheumatoid arthritis, pointing towards the possibility that these antibodies directed against periodontopathic bacteria could be important in the etiopathogenesis of rheumatoid arthritis.[10]
2. Porphyromonas gingivalis is an important periodontopathic bacteria that possesses a unique microbial enzyme, peptidyl arginine deaminase (PAD), which is the human equivalent of this enzyme and has been

Table 1: A summary of the effects of drugs that target both rheumatoid arthritis and periodontitis

Drugs	Cells affected	Effect	Clinical effect
Tetracyclins	Oral microorganisms and macrophages, fibroblasts	↓ endotoxins Inhibit lysosomal enzymes, MMPs	↓ periodontal and joint tissue destruction
Bisphosphonates	Osteoclasts	Inhibit lysosomal enzymes	↓ bone destruction in alveoli and joints
NSAIDs	Macrophages	Prostaglandins(PGE2)	↓ alveolar bone destruction Symptomatic relief in rheumatoid arthritis
CMTs	Macrophages, fibroblasts, endothelial cells	Inhibit lysosomal enzymes, MMPs, NO synthesis	↓ periodontal and joint tissue destruction
Ornidazole	Oral microorganisms	-	↓ periodontal destruction and ↓ disease activity in rheumatoid arthritis.
Osteoprotegrin	Osteoclasts	Inhibit RANK-RANKL interaction	↓ bone destruction in alveoli and joints
CLA	Osteoclasts	Suppress RANKL signaling	Reduce bone resorption

CMT - Chemically modified tetracyclins, CLA – Conjugated linoleic Acid, MMP - Matrix Metalloproteinase, NSAID - Non-steroidal anti-inflammatory drugs, NO - Nitric oxide, RANK - Receptor activation of nuclear factor kappa B, RANKL- Receptor activation of nuclear factor kappa B ligand

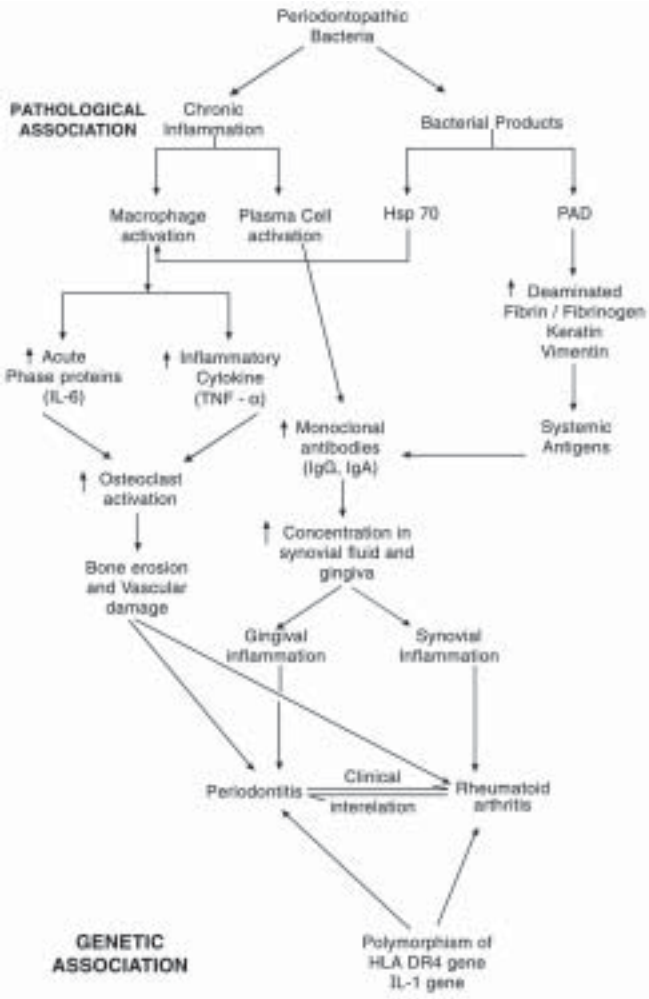

Figure 1: Possible mechanism of pathological and genetic association between rheumatoid arthritis and periodontitis

implicated as a susceptibility factor for rheumatoid arthritis. It has been proposed that individuals with periodontal infection with porphyromonas gingivalis are exposed to antigens generated by PAD such as de-aminated fibrin/fibrinogen, keratin, and vimentin. These antigens become systemic immunogens leading to the production of rheumatoid factor and local inflammation of both gingiva and synovium.[11]

3. Antibodies against heat shock proteins (hsp 70 Ab) of P-melaninogenica and P-intermedia have been found to be raised in the periodontal tissue as well as the synovial tissue of patients with rheumatoid arthritis. It has also been shown that when the hsp 70 expression is induced with certain stress-stimulating factors, pro-inflammatory cytokines are induced in the synovium of these patients[12] further pointing towards the etiopathogenetic relation between rheumatoid arthritis and periodontitis.
4. Genes on the human leukocyte antigen (HLA) region remain the most powerful disease risk genes in the patients of both rheumatoid arthritis and periodontitis. HLA-DR4 antigens and their subtypes are directly associated with both these diseases.[13] This genetic association between the two diseases also indicates a potential connection between rheumatoid arthritis and periodontitis.
5. Studies of the cytokine profile of patients with rheumatoid arthritis and periodontitis has shown that patients of both these diseases have raised titters of IL-10, IL-1α, tnf-α, LT-α, and low titters of auto antibodies to IL-1α and IL-6.[14] Similar patterns of blood cytokine profile in both the diseases also point toward a common underlying disregulation of the inflammatory and immune response.
6. L-1 cytokines are key mediators of immune responses, inflammation, and tissue destruction in both the diseases. Increased levels of IL-1B are found in the synovial tissue nacrophages and in the periodontal crevicular fluid in patients with rheumatoid arthritis and periodontitis, respectively. A recent study demonstrated that the polymorphism of the IL-1 gene affected the cytokine profile in patients of both periodontitis and chronic arthritis like rheumatoid arthritis.[15]
7. Experimentally induced inflammatory arthritis in rats was found to be associated with elevated levels of tissue matrix metalloproteinases, tumor necrosis factor –ά, and interleukin-1 beta in both the synovial tissue and the gingival tissue.[16] This study also shows that the two diseases could be closely related through a common dysfunction of fundamental inflammatory mechanisms.

If there is validity to the biological base for linking aspects of rheumatoid arthritis and periodontitis then therapies that concordantly target these two diseases will be effective in reducing the levels of proinflammatory cytokines and destructive proteases implicated in the pathogenesis of both diseases.

DUAL PURPOSE THERAPIES BASED ON BIOLOGICAL LINKS

1. Tetracyclines and its analogues: The tetracyclines are a group of broad-spectrum antimicrobial agents. They are active against a number of gram-positive and gram-negative bacteria. In the 1980s, periodontal research revealed that tetracyclines also inhibited collagenase activity.[17] Collagenases are a large family of enzymes that breakdown macromolecules in the connective tissue; they include matrix metalloproteinases (MMPs). Tetracyclines reduce the activity of MMPs by depriving them of divalent cations, which are cofactors necessary for their activity. They chelate these ions thereby reducing their protein degrading activity.[18] This action of tetracyclines is observed at sub antimicrobial doses.[19] Enhanced activity of the MMP has been demonstrated in synovial fluid and synovial fibroblasts of patients with rheumatoid arthritis and is partly responsible for joint destruction in these patients.[20] Tetracyclines by virtue of their anti-MMP activity are useful in patients with rheumatoid arthritis. Several clinical trials have shown that minocycline administration in patients with rheumatoid arthritis was associated with significant reduction in disease activity.[21]
   Soft and hard tissue destruction in periodontitis is partly due to bacterial virulence factors/enzymes and partly due to MMPs.[22] Tetracyclines and their analogues have been shown to be useful in the treatment of patients with rapidly progressive and refractory periodontitis.[23] They act both by suppressing the growth of putative microorganisms implicated in periodontitis and by decreasing the destruction of collagen in gingival, periodontal ligament and alveolar bone by inhibiting MMPs in these patients.[22]
2. Nonsteroidal anti-inflammatory drugs (NSAIDs): The principal mechanism by which NSAIDs act is by inhibition of cycloxygenase—the enzyme responsible for the biosynthesis of prostaglandins. Studies have shown that periodontally diseased tissues have higher prostaglandin levels, especially prostaglandin E_2, than in healthy tissue.[24] *In vivo* studies have also shown that bone resorption in periodontitis is mediated in part by prostaglandins, showing that these may be important mediators of periodontal disease.[25] If prostaglandins are important mediators of bone resorption in periodontitis, the use of NSAIDs should be effective in preventing inflammation-induced bone loss. Both animal and human studies have demonstrated that inhibiting prostaglandin E2 synthesis with NSAIDs has been associated with unequivocal therapeutic efficacy in patients with periodontitis.[26] Current protocols for the prevention of periodontal disease require long term use of NSAIDs.
   NSAIDs find their chief clinical application as anti-inflammatory agents in the treatment of rheumatoid arthritis to reduce pain and inflammation. It has been documented that certain NSAIDs can directly inhibit the activation and function of neutrophils.[27] They also inhibit TNF-α release from monocytes and non-killer (NK) cells.[28] These cycloxygenase independent effects may also contribute to the efficacy of NSAIDs in the treatment of rheumatoid arthritis.
3. Bisphosphonates: Osteoclasts are responsible for the absorption and removal of bone. Agents that affect osteoclast function may be effective in the treatment of periodontitis and rheumatoid arthritis. A class of drugs known as bisphosphonates inhibits osteoclasts. They are incorporated into the bone and incapacitate osteoclasts thereby inhibiting lysosomal enzyme transport and secretion by osteoclasts.[29] Focal bone damage and generalized bone loss are features of rheumatoid arthritis. Studies have shown that new-generation bisphosphonates, like zoledronic acid, reduced the development of new bony erosions in patients with rheumatoid arthritis suggesting a structural benefit with bisphosphonate therapy in these patients.[30]
   Alveolar bone loss is an important complication of the inflammatory process in periodontitis. Markers of inflammation like TNF-α stimulate osteoclastic bone resorption in these patients. Bisphosphonate therapy is useful in them as they inhibit bone resorption and increase bone mass. Bisphosphonate treatment also improves the clinical outcome in patients with periodontitis and may be an important adjunctive treatment for periodontitis therapy for prevention of bone loss.[31]

EMERGING THERAPIES

1. Ornidazole: A synthetic, nitroimidazole with potent antiprotozoal and antibacterial activity. Ornidazole has good activity against most of the periodontopathic bacteria and is a commonly used drug for the treatment of periodontitis.[32] The usefulness of ornidazole has also been documented in patients with rheumatoid arthritis though its mechanism of action is not known. Ogrendik, *et al*.[33] showed that the administration of ornidazole in patients with active rheumatoid arthritis was associated with a significant reduction in pain, duration of morning stiffness, erythrocyte sedimentation rate (ESR) and C-reaction protein levels. An overall reduction in disease activity was observed. Orinidazole was well tolerated in these patients at a dosage of 500–1000 mg/day with few adverse effects, such as headache, dry mouth, and nausea.

2. Chemically modified tetracyclines (CMTs): These are the drugs that were developed to eliminate the antimicrobial properties of tetracyclines while retaining their non antimicrobial properties by modifying the tetracyclic naphthacene carboxamide ring of tetracyclins.[34] CMTs inhibit the synthesis of MMPs.[35] Non antibiotic analogues of doxycyclin (CMT-3) and minocyclin (CMT-8) have been shown to be potent inhibitors of osteoclastogenesis *in vitro*.[36] CMT-8 has also been shown to exert anti-inflammatory effects by inhibiting nitric oxide (NO) synthesis, and it can also modify cell viability by exerting a strong apoptotic activity.[37] Such CMTs may reduce tissue breakdown and bone resorption in rheumatoid arthritis and periodontitis and might emerge as future disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis.
3. Osteoprotegrin (OPG): Recent evidence shows that the interaction between the receptor activation of nuclear factor kappa B ligand (RANKL) and its receptor activator (RANK) has an essential role in the activation of osteoclast and bone resorption.[38] OPG is a naturally occurring high affinity soluble decoy receptor for RANKL. It inhibits RANKL interaction with RANK thereby inhibiting osteoclast activation as a result of this interaction.[39] RANKL appears to be the important pathogenetic principle that is responsible for the destruction of bone matrix in patients with both rheumatoid arthritis and periodontitis.[3,39] It has also been documented that OPG expression on synovial lining cells is deficient in patients with rheumatoid arthritis with active synovitis and in gingival cervical fluid in patients with periodontitis.[38,40] In view of the ability of OPG to block RANK-RANKL interaction and osteoclast activation, it may have a therapeutic role in conditions where bone destruction is a major sequel of chronic inflammation such as rheumatoid arthritis and periodontitis.
4. Conjugated linoleic acid (CLA):[41] It has been found to be an important inhibitor of osteoclastogenesis. It acts by modulating the RANKL signaling pathway. CLA has also been shown to positively influence calcium and bone metabolism. Thus, it may have important therapeutic implications in the treatment of inflammatory diseases associated with bone destruction.

CONCLUSION

The past few years have witnessed an increase in research evidence suggesting an association between periodontitis and an increased risk of rheumatoid arthritis. How are the two diseases linked? Probably the inflammatory mediators and microbial products (endotoxins) are the likely conduits. Inhibition of common mediators and effector molecules such as MMPs can reduce the severity of both of these diseases. However, there is still a clear need for methodologically rigorous observational studies and therapeutic trials in this area.

REFERENCES

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005;4:130-6.
2. Woolley DE, Crossley MJ, Evanson JM. Collagenases at sites of cartilage erosion in the rheumatoid joint. Arthritis Rheum 1977;20:1231-9.
3. Haynes DR, Crotti TN, Capone M, Bain GI, Atkin GJ, Findlay DM. Osteoprotegerin and receptor activator of nuclear factor kappaB ligand (RANKL) regulate osteoclast formation by cells in the human rheumatoid arthritic joint. Rheumatology (Oxford) 2001;40:623-30.
4. Chu CQ, Field M, Allard S, Abney E, Feldmann M, Maini RN. Detection of cytokines at the cartilage/ pannus junction in patients with rheumatoid arthritis: Implications for the role of cytokines in cartilage destruction and repair. Br J Rheumatol 1992;31:653-61.
5. Papapanau PN. Periodontal disease: Epidemiology. Ann Periodontol 1996;1:1-36.
6. Takashiba S, Naruishi K, Murayama Y. Perspective of cytokine regulation for periodontal treatment: Fibroblast biology. J Periodont 2003;74:103-10.
7. Mercado F, Marshall RI, Klestov AC, Bartold PM. Is there a relationship between rheumatoid arthritis and periodontal disease? J Clin Periodontol 2000;27:267-72.
8. Mercado FB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. J Periodontol 2001;72:779-87.
9. Slots J. Systemic antibiotics in periodontics. J Periodont 1996;67:831-8.
10. Ogrendik M, Kokino S, Ozdemir F, Bird PS, Hamlet S. Serum antibodies to oral anaerobic bacteria in patients with rheumatoid arthritis. MedGenMed 2005;7:2-10.
11. 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. Inflammation 2004;28:311-8.
12. Schett G, Redlich K, Xu Q, Bizan P, Gröger M, Tohidast-Akrad M, *et al.* Enhanced expression of heatshock protein 70 (hsp 70) and heat shock factor 1 (HSF1) activation in rheumatoid arthritis synovial tissue: Differential regulation of expression and hsf1 activation in synovial fibroblasts by proinflammatory cytokines, shear stress, and anti-inflammatory drugs. J Clin Invest 1998;102:302-11.
13. 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 epitopes. Ann Rheum Dis 2006;65:905-9.
14. Havemose-Poulsen A, Sørensen LK, Stoltze K, Bendtzen K, Holmstrup P. Cytokine profiles in peripheral blood and whole blood cell cultures associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol 2005;76:2276-85.
15. Havemose-Poulsen A, Sørensen LK, Bendtzen K, Holmstrup P. Polymorphism within the IL-1 gene cluster: Effects on cytokine profiles in peripheral blood and whole blood cell cultures of patients with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol 2007;78:475-92.
16. Rammamurthy NS, Greenwald RA, Celiker MY, Shi EY. Experimental arthritis in rats induces biomarkers of periodontitis which are ameliorated by gene therapy with tissue inhibitor of matrix metalloproteinases. J Periodontol 2005;76:229-33.
17. Golub LM, Rammamurthy NS, McNamara TF, Gomes B, Wolff M, Casino A, *et al*. Tetracyclins inhibit tissue collagenase activity: A new mechanism in the treatment of periodontal disease. J Periodontol Res 1984;19:651-5.
18. Rifkin BR, Vermillo AT, Golub LM. Blocking periodontal disease progression by inhibiting tissue destructive enzymes: A potential therapeutic role for tetracyclins and their chemically modified analogues. J Periodontol 1993;64:819-23.
19. Choi DH, Moon IS, Choi BK, Park JW, Kim YS, Choi SH, *et al*. Effects of sub-antimicrobial dose of doxycycline therapy on cervicular fluid MMP-8 and gingival tissue MMP-9, TIMP-1 and IL-6 levels in chronic periodontitis. J Periodontol Res 2004;39:20-6.
20. Fiedorczyk M, Klimiuk PA, Sierakowski S, Gindzienska-Sieskiewicz E, Chwiecko J. Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with early rheumatoid arthritis. J

Rheumatol 2006;33:1523-9.
21. Stone M, Fortin PR, Pacheco-Tena C, Inman RD. Should tetracycline treatment be used more extensively for rheumatoid arthritis? Meta analysis demonstrates clinical benefit with reduction in disease activity. J Rheumatol 2003;30:2112-22.
22. Sorsa T, Tjaderhane L, Konttinen YT, Lauhio A, Salo T, Lee HM, *et al*. Matrix metalloproteinases: Contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. Ann Med 2006;38:306-21.
23. 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.
24. Zubery Y, Dunstan CR, Stony BM, Kesavalu L, Ebersole JL, Holt SC, *et al*. Bone resorption caused by three periodontolal pathogens in vivo in mice is mediated in part by prostaglandins. Infect Immun 1998;66:4158-62.
25. EL attar TM, Lin HS. Prostaglandins in gingival of patients with periodontal disease. J Periodontol 1981;53:16-20.
26. Salvi GE, Williams RC, Offenbacher S. Nonsteroidal anti-inflammatory drugs as adjuncts in the management of periodontal diseases and peri-implantitis. Curr Opin Periodontol 1997;4:51-8.
27. Pillinger MH, Capodici C, Rosenthal P, Kheterpal N, Hanft S, Philips MR, *et al*. Mode of action of aspirin-like drugs: Salicylates inhibit erk activation and integrin dependent neutrophil adhesion. Proc Natl Acad Sci USA 1998;95:14540-5.
28. Gunella G, Bardelli C, Spina S, Fresu LG, Viano I, Brunelleschi S. Anti-inflammatory drugs and tumor necrosis factor alpha production from monocytes: Role of transcription factor NF-Kappa B and implication for rheumatoid arthritis therapy. Eur J Pharmacol 2004;6:199-208.
29. Breuil V, Euller-Ziegler L. Bisphosphonate therapy in rheumatoid arthritis. Joint Bone Spine 2006;73:349-54.
30. Jarrrtt SJ, Conaghan PG, Sloan VS, Papanastasiou P, Ortmann CE, O'Connor PJ, *et al*. Preliminary evidence for a structural benefit of the new bisphosphonate zoledronic acid in early rheumatoid arthritis. Arthritis Rheum 2006;54:1410-4.
31. Lane N, Armitage GC, Loomer P, Hsieh S, Majumdar S, Wang HY, *et al*. Bisphosphonate therapy improves the outcome of conventional periodontal treatment: Results of a 12-month randomized placebo controlled study. J Periodontol 2005;76:1113-22.
32. Kamma JJ, Nakou M, Mitsis FJ. The clinical and microbiological effects of systemic ornidazole in sites with and without subgingival debridement in early-onset periodontitis patients. J Periodontol 2000;71:1862-73.
33. Ogrendik M, Hakguder A, Keser N. Treatment of rheumatoid arthritis with ornidazole: A randomized double blind, placebo-controlled study. Rheumatology (Oxford) 2006;45:636-7.
34. Golub LM, Soummalainen K, Sorsa T. Host modulation with tetracyclins and their chemically modified analogues. Curr Opin Dent 1992;2:80-90.
35. Sapadin AN, Fleischmajer R. Tetracyclins: Nonantibiotic properties and their clinical implications. J Am Acad Dermatol 2006;54:258-65.
36. Holmes SG, Still K, Buttle DJ, Bishop NJ, Grabowski PS. Chemically modified tetracyclins act through multiple mechanisms directly on osteoclast precursors. Bone 2004;35:471-8.
37. D'Agostino P, Ferlazzo V, Milano S, La Rosa M, Di Bella G, Caruso R, *et al*. Anti-inflammatory effects of chemically modified tetracyclines by the inhibition of nitric oxide and interleukin-12 synthesis in J774 cell line. Int Immunopharmacol 2001;1:1765-76.
38. Mogi M, Otogoto J, Ota N, Togari A. Differential expression of RANKL and OSteoprotegerin in gingival crevicular fluid of patients with periodontitis. J Dent Res 2004;83:166-9.
39. Nakashima T, Wada T, Penninger JM. RANKL and RANK as novel therapeutic targets for arthritis. Curr Opin Rheumatol 2003;15:280-7.
40. Haynes DR, Barg E, Crotti TN, Holding C, Weedon H, Atkins GJ, *et al*. Osteoprotegerin expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthrithropathies and osteoarthritis and normal controls. Rheumatology 2003;42:123-34.
41. Rahman MM, Bhattacharya A, Fernandes G. Conjugated linoleic acid inhibits osteoclast differentiation of RAW264.7 cells by modulating RANKL signaling. J Lipid Res 2006;47:1739-48.

How to cite this article: Modi DK, Chopra VS, Bhau U. Rheumatoid arthritis and periodontitis: Biological links and the emergence of dual purpose therapies. Indian J Dent Res 2009;20:86-90.

Source of Support: Nil, **Conflict of Interest:** None declared.