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Periodontitis:A Chronic Inflammatory Disease Closely Associated with Rheumatoid Arthritis

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Abstract

Demonstrated researches have established close association in the pathophysiology between periodontitis (P D) and rheumatoid arthritis (R A). However, PD has purely bacterial etiology where as the etiology regarding RA is still unclear. Evidences have established that bacterial strains are responsible that trigger host for the development of RA. It has also been determined that PD is more severe and frequent in patients with RA which closely indicates association between the two inflammatory conditions.Periodontitis is a chronic tissue destructive condition in which tooth and supporting collagen fibers of the ligament and bones of jaws are broken down mainly by hosts by the reaction of immune inflammatory response. The relationship between periodontitis and other inflammatory diseases such as rheumatoid arthritis have been dealt with in some studies. Instead of their different etiology, similar mechanism of tissue destruction has been described in this article.

Key Words: C-reactive proteins, Immune response, Inflammation, Periodontitis,

Rheumatoid Arthritis

Introduction

This has been a debate over years that periodontitis (PD) and rheumatoid arthritis (RA) has a close association as both are chronic inflammatory diseases and it has also been suggested that the treatment modalities for rheumatoid arthritis may also be useful for the treatment of periodontitis.[1]

In the early 19th century the American physician and politician, Benjamin Rush described the association between RA and PD and proposed that tooth extraction is the cure for the severity and symptoms of RA. But this was no longer retained when Cecil and coworkers in the late 1930's said that tooth eradication is not a treatment of choice for RA. In 1952 American Medical Association also seconded Cecil's and coworkers statement. [1]

However, PD is a chronic inflammation and the commonest of all oral diseases; it causes destruction to the supporting tissues of the peridontium i.e. the bone and the gingiva. Gram negative Porphyromonas gingivalis has been identified as the primary culprit that causes PD. It mediates host immune response factors such as interleukin IL-1, interleukin IL-6 and tumor necrosis factor (TNF-α). Other species which may be secondary to Porphyromonas gingivalis are Prevotelle intermedia, Tannerella forsythia and Aggregatibacter Actinomycetem-Comitans. [1, 2, 3, 4, 5, 6]

PD and RA are similar to each other on cellular and molecular grounds. This has been explained by the concept of monocytic cytokine response in RA and same has also been accepted for PD. The regulation of many genes in humans is activated by the response of monocytic cytokine complex, and has been represented to HLA-DR (human leukocyte antigen) region in chromosomes in TNF-α gene. Thus, chronic inflammatory diseases are interconnected to each other through the HLA complex.[3]

PD leads to the accumulation of inflammatory cells (B- lymphocytes, T- lymphocytes,

monocytes and neutrophils) and causes tissue edema, endothelial cell proliferation and matrix degradation resulting in severe clinical manifestations. Gingivitis, periodontitis, aggressive periodontitis, necrotizing periodontitis and periodontitis associated with endodontic lesions and systemic diseases can be differential in diagnosing periodontal disease. [1, 7]

RA is an autoimmune disease and its main etiology is not well understood. It is the commonest of all joint disorders which leads to polyarthritis, synovial inflammation and tissue destruction. It shows 5% higher prevalence in females than in males in the total world population. Age plays a major role and secondary to age, the environmental, hormonal and infectious conditions are the co-factors which may also be involved in the progression of RA. [1, 8]

RA is a chronic inflammatory disease which involves synovial joints of the body. Over decades the researches have established crosslinking association between RA and PD. Also, researches have shown the more frequent development of PD in patients with RA when compared to that of nonRA individuals. Moreover when comparing symptoms, patients with PA show low jaw bone density, widened periodontal ligament space and tooth loss. Patients with RA have shown swollen joints, increased C-reactive proteins and erythrocyte sedimentation rate. Other risk factors in association of RA and PD are socioeconomic status, alcohol consumption, body mass and poor oral hygiene.[9]

Many researchers have postulated that patients with long standing RA are more likely to develop PD. Moreover, PD, in addition to RA has also been associated with other systemic diseases like diabetes, atherosclerosis, myocardial infarction, stroke, lung diseases, gastrointestinal diseases (Crohn) and osteoporosis and skin diseases. [1, 2, 8]

Assessment of general pathology can easily be made by a variety of biomarkers which are known to be very effective e.g. blood, serum, cultures, bone marrow etc. But in oral pathologies, acute phase of periodontal condition can easily be assessed by means of evaluating pocket depths by probing, plaque index, bleeding on probing and radiographs. But in chronic inflammatory diseases, recent studies have shown that not only the above mentioned biomarker can relate to

any disease for the diagnostic purpose, saliva also can be very helpful in diagnosing pathological measures in which immunoglobulins, interleukin (IL)-Iβ, C- reactive protein, matrix metalloproteinase (MMP-8) and TNF-α have been identified as essential biomarkers. Elevation of these components in the serum of the person shows establishment of the chronic inflammatory disease, such as PD or RA. These biomarkers can be easily identified by taking patient's saliva. as seen in other studies.[10, 11]

Many studies shown that patients with moderate to severe periodontitis are at a higher risk to develop rheumatoid arthritis or vice versa.[12, 13]

The aim of this review is to describe the detailed relationship between periodontitis and rheumatoid arthritis on the basis of immune response, genetics, laboratory analysis, and clinical symptoms.

BIOFILM: the significance of periodontal disease

The newly formed biofilm, dental biofilm or pellicle layer can also be referred to as healthy plaque which contains peroxidase, produce by the salivary glands. The function of the enzyme is to remove hydrogen peroxide producing toxic bacteria and decrease the acid production in the the dental biofilm. Therefore, it reduces plaque formation and destruction to the gingival and periodontal tissues. Biofilm is naturally present on the smooth surfaces of a tooth. It is immediately formed within few minutes after mechanical tooth brushing. This layer contains both acid producing and acid tolerating bacteria which attach themselves by means of pili, glycocalyx or fimbriae according to their structure on the tooth surfaces. Having a complex structure, metabolically formed bacteria not only provide a medium of adherence but are also highly resistant to the host defense mechanism as well as antibiotics due to their subgingival location. If this layer is not removed and retained to the tooth surfaces for a longer period of time, it is then transformed into a pathogenic plaque, which consequentially leads to periodontal disease. [2, 11, 13, 14, 15]

The pathogenic biofilm has a paradoxical impact on the host's immune system and leads to non

reversible attachment loss; this may cause the destruction of the periodontal tissues, subsequent tooth mobility and ultimately tooth loss. The etiology of any acute or chronic periodontal condition depends on the aggregation of microflora by means of the biofilm. This film constitutes gram negative and facultative bacterial species and their by products which has tissue degrading properties. [12, 13]

Production of acidogenic byproducts and tissue injury initiates the activation of osteoclastic activity by means of tissues degrading enzymes, leucotoxins and acid phosphatases which ultimately cause attachment loss. [2]

Moreover, the host defense mechanism is inhibited by lipopolysaccharides and proteoglycans which are the integral part of the bacterial cell wall. Continuation of the process activates the release of cytokines which ultimately results in bone resorption and tooth loss. [2]

Smoking

Researchers have shown that smoking is highly susceptible to RA progression but only in individuals who are the carriers of autoantibody- positive RA characterized by the presence of ACPAs (anti- citrullinated protein/peptide antibody). Interrelationship between oral hygiene, smoking in association with RA, ACPA and immune response to P.gingavalis has been determined. Smoking and poor oral hygiene increases the risk of developing RA via actions of nicotine on inflammatory cytokine, MMP-3 and P.gingavalis gene expression. It is established that smoking and poor oral hygiene found out to have a close association for developing RA. [2]

Many researches has been postulated explaining the adverse effects of tobacco use of any kind such as cigarette , pipes, cigar etc which not only affect periodontal health but also affect, ongoing periodontal surgery, regenerative procedures and also dental implants. Microbial flora and host defense play a very critical role in the progression of periodontal destruction in smokers.[16]

Hence, smoking not only affects the periodontal health status or therapies but it also has harmful

effects on oneself behavior, environmental conditions, systemic health and adverse genetic influences as shown in fig.1 [16] Smoking and other tobacco use might influence the central pathway of bacterial plaque and the host response to the plaque which may lead to periodontal breakdown. IL-1B, interleukin-1B. Fig 1[16]

Salivary biomarkers; as a diagnostic tool

Majority of researches have explained in assessing periodontal disease by using oral fluids, saliva and gingival crevicular fluid. As known saliva is secreted from submandibular, sublingual, parotid and other minor salivary glands which maintain the integrity of the oral environment. Saliva from both the healthy and unhealthy individuals explains the health status and can easily be used to distinguish between both the strains. Salivary biomarkers are the mirror images of the patient's health evaluation in identifying not only in the establishment of a particular disease but also the severity of dysfunction.[11]

These biomarkers release from both the major and minor salivary glands and are basically enzymes and proteins. These biomarkers have defensive properties which also maintain the integrity of the oral environment. [11]

These markers are broadly classified into three groups: specific which contains immunoglobulins (IgA, IgM, and IgG), non-specific which are proteins (mucins, lactoferrin and histatin) and enzymes (peroxidase and lysozyme) and systemic, C-reactive proteins released from liver.[11]

However with respect to saliva, gingival crevicular fluid may also help in diagnosis as variety of inflammatory mediators has been obtained to describe the established diseased condition. This gingival crevicular fluid is secreted from the gingival plexus of blood vessels in the gingival corium, epithelial lining of the dentogingival space.[11]

The diagnostic importance of saliva and gingival crevicular fluid is used to monitor the onset and progression of the periodontal disease.[11]

Elevated levels of all the components mentioned in table 1 for eg specific Immunoglobulins

(IgA, IgM, IgG) and non-specific like mucins, lysozyme, lactoferin, peroxidase, and systemic c reactive proteins are subjective to the establishment of the inflammatory process and shows correlation between the periodontal diseases with its type of severity.[11] (Table 1)

Potential inflammatory immune mediation in PD and RA

The immune system has two fundamental systems which get activated in response to an invading pathogen. Among these two universal and closely coordinated systems one is humoral immunity which is mediated by T and B lymphocytes and the other is innate immunity, activated by cytokines, chemokines, phagocytic cells and killer cells.[17]

As discussed earlier that gingivitis is an inflammatory process occurs in response to bacterial biofilm and is characterized by increased blood flow, vascular permeability and incorporation of inflammatory cells at the site of infection.[12]

The whole inflammatory cascade becomes activated by the cytokine release and their byproducts which occurs by the presence of bacterial lipopolysaccharide.[7] Furthermore, low levels of tissue inhibitor metalloproteinase (TIMS) and increased levels of matrix metalloproteinase (MMPs) and PGE_2 describes the active stage related to immune mediation in PD. Neutrophils are the major cells for the release of MMPs from gingival crevicular fluid due to host response mediation. These are the enzymes and are responsible for the destruction in the periodontal tissues. It is recognized that two main MMPs are involved in the immune reactions and are MMP-8, responsible for the degradation of interstitial collagen and MMP-9, responsible for degrading extracellular matrix proteins.[18]

Cytokines are the major mediators in the progression of PD and RA. These cytokines are divided into two groups on the basis of their functional origin. The first is derived from T-cell and are IL-2, IL-3, IL-4, and interferon gamma. Whereas, second potent group is derived from fibroblasts and macrophages and are IL-1, IL-6, colony stimulating factor1 and tumor necrotizing factor-α (TNF-α). These all result in the production of increased prostaglandin production and matrix degrading proteases, resulting in bone resorption.[12]

Therefore, in RA, activation of the second group results in all signs of inflammation i.e. redness, pain, swelling and loss of function and initiate the production of C-reactive protein, the molecules of this protein adhere them on the endothelial cells and neutrophils, diapedesis occurs and induce interleukin-1 activation. This activation in turns stimulates synoviocytes and collagenase, resulting in cartilage destruction and leads to osteolysis.[12]

However, in PD activation of PGE_2, MMPs and TNF-α cause osteoclastic activity which results in severe pathologic condition in PD. In RA, MMPs are also released within the cytokine cascade by the stimulation of synoviocytes by IL-1 which results in cartilage destruction.[12]

C- Reactive proteins (CRP)

In 1930's Tillet and Francis discovered C- reactive proteins (CRP) in the patients of pneumonia in serum. They are synthesized in liver and are named due to their ability to react with C-polysaccharide derived from pneumococcal cell walls. The plasma concentration increased during the chronic inflammatory process.[19]

PD is associated with increased level of CRP and fibrinogen which can be a cause of coronary heart disease and other systemic chronic inflammatory diseases (diabetes mellitus, stroke, atherosclerosis and pregnancy outcomes). The mean level of CRP is 1.05mg/l and was decreased to 0.7mg/l after the periodontal treatment. Increased level of fibrinogen and CRP can be indication for developing PD with might cause systemic manifestation due to the similar rise. However, this monitoring is useful for public health workers so that the prevalence of chronic inflammatory systemic disease can be controlled.[20, 21, 22]

Role of RANKL in Osteoclastogenesis

RANKL was discovered first in cytokines and is a pro inflammatory cytokine; and initiates osteoclastogenesis. This cytokine has been given importance for evaluating its increased production during the osteoclastic activity. Studies' being conducted during 1970's found lymphokine produced by T-cell in the inflammatory process which was later termed as RANKL,

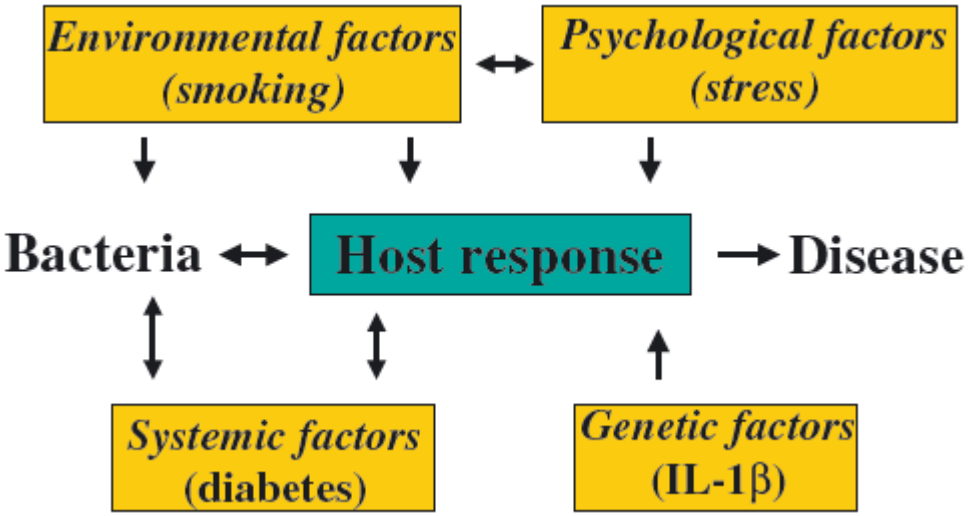

Fig. 1. Modification of the model of the interplay of etiologies, risk factors and risk indicators, proposed by Kenneth Kornman and others to play a role in the pathogenesis of periodontal diseases. Smoking and other tobacco use might influence the central pathway of bacterial plaqueand the host response to the plaque which may lead to periodontal breakdown. IL-1B, interleukin-1B.[16]

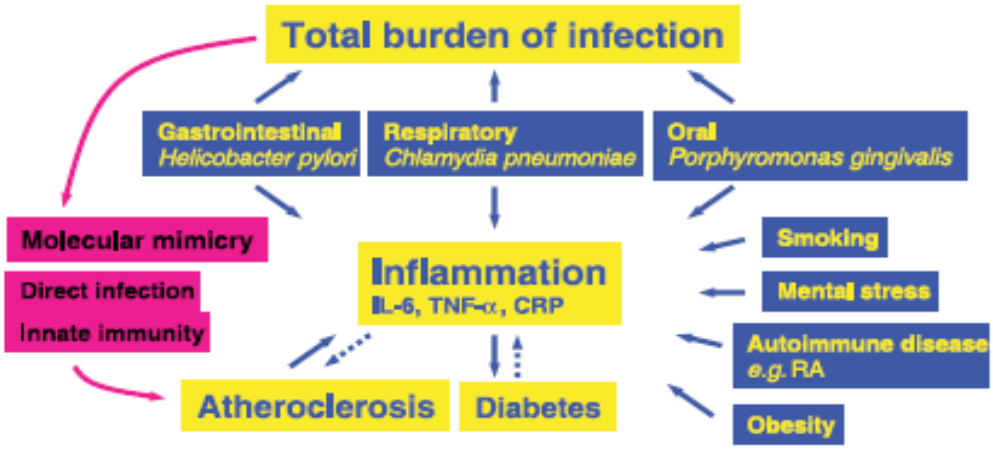

Fig 2: Correlation between periodontitis with other systemic manifestations. [24]

Markers	**Relationship with the periodontal disease**	**Type of periodontal disease**
Specific		
Immunoglobulins (IgA, IgM, IgG)	Interfere in adherence and bacterial metabolism/ increased concentration in saliva of periodontal patients.	Chronic and aggressive
Non-specific		
Mucins	Interfere with the colonization of Aggregatibacter Actinomycetemcomitans.	Aggressive
Lysozyme	Regulates biofilm accumulation.	Chronic
Lactoferrin	Inhibits microbial growth/increased correlation with A. actinomycetemcomitans.	Aggressive
Histatin	Neutralizes lipopolysaccharide and enzymes known to affect the periodontium.	Chronic and aggressive
Peroxidase	Interferes with biofilm accumulation/increased correlation with periodontal patients.	Chronic
Systemic		
C-reactive protein	Increased correlation found in serum and saliva of periodontal patients.	Chronic and aggressive

Table 1: Salivary biomarkers; as a diagnostic tool.[11]

where RANK is a receptor for lymphokine (L). Research had been carried out in knockout mice lacking both RANK and RANKL which later showed that they are not only present as osteoparotic phenotypes but also lacking peripheral lymphnodes. Hence it proved that both RANK and RANKL are fundamental in the process of osteoclastogenesis. Furthermore soluble decoy receptor osteoprotogrin (OPG) contributes for the skeletal remodeling. Thus individuals involved in the disease state were found to have low levels of (OPG) and higher level of RANK and RANKL in the human subjects. [23]

Correlation between periodontitis with other systemic manifestations

Over the recent decade, studies have also explained the association between PD with systemic manifestation such as diabetes, respiratory dysfunction, osteoporosis, low birth weight, coronary heart disease and stroke which has come under consideration. Nevertheless, certain researches have been postulated explaining C-reactive proteins, T-cells, heat shock proteins (HSPs) and Porphyromonas gingivalis in such individuals. It shows that oral infections may also take part in the development of systemic risk factors. It is essential that the control of oral diseases is as essential to be controlled as systemic diseases which manifest in the oral cavity.[11, 24]

Chronic inflammatory diseases are found to be the most prevalent condition in the world's population which constitutes around 10%-15% of the total world's population. Among all the oral diseases, chronic periodontitis found to be most evident which shows significant role for systemic manifestation. Recent researches have shown that almost 50% of the population suffering from cardiovascular disease has not the traditional way of death e.g. smoking, obesity, high blood pressure, diabetes and hypercholestrolemia. Therefore it is very much necessary to evaluate all the risk factors even the oral hygiene and its duration for the morbidity and mortality.[11, 24] (Fig.2)

Diagnostic parameter for periodontal disease:

The diagnostic parameters useful in the clinical practice today includes probing depths, bleeding

on probing, clinical attachment levels, plaque index and radiographs, this has been in use in the past also for more than years. The National Institute of Dental and Craniofacial Research (NIDCR) in response to the above discussed tools has proposed that oral fluid assessment in the diagnosis of periodontal diseases e.g. saliva, gingival crevicular fluid (GCF), and mucosal transudate for the confirmation of oral and systemic manifestation. The objective for the evaluation of the biological variants is not only for the detection of a particular disease but also the severity of an illness. These variants are derived from the proteins of the host origin enzymes, immunoglobulins, phenotype markers (PMNs), bacteria and bacterial by products. Because periodontal manifestation is a complex illness, a single biomarker strand will not be sufficient for establishing a periodontal condition.[11, 25]

Conclusion

In this review the remarkable relevance between two chronic and deliberating inflammatory diseases has been proposed and the prevalence of moderate to severe periodontitis is significantly higher in patients with RA.

Following points in reference to each other have been discussed in this article:

- Biofilm serves as a source of initiating inflammatory cascade seen in RA, however evidence has established that IL-1β, MMP-8 and TNF-α are clearly influenced by the local periodontal and environmental factors.
- Presence of periodontal pathogens are highly susceptible for developing RA. Furthermore among many species P. gingivalis is found to have close association in the etiology of periodontitis and RA as they may trigger the autoimmune reactions.
- Association of periodontitis with other systemic manifestations like cardiovascular disease and diabetes share the same genetic aberration but warrants further detailed investigations.

Future considerations

The research suggests an injurious effect on periodontal heath which might influence the

relationship between the two deliberating inflammatory diseases. Immunogenetics involved in the progression of vice versa determines the similar degree of destruction in the periodontium and joints of the body. Studies have shown that the initiation and progression of RA and PD occurs due to inappropriate response of inflammatory cytokines.

However following considerations have been proposed for the inflammatory diseases to be viewed in detail for further firm association between the two conditions: RANKL expression genes in GCF and gingival tissues should be analyzed deeply.

Interlinking between the peripheral blood cytokines of disease strains with non disease individuals should be studied in detail, not only for knowing the interlinking facts between RA and PD but also for the better prognosis of the strains.

References

1. Rutger GP. Rheumatoid arthritis and periodontitis- inflammatory and infectious and connections: Review of the literature. J Oral Microbio 2012; 4: 01-7.
2. Jacqueline D, Nicole P, Gerd RB, Frank B. The association between rheumatoid arthritis and periodontal disease. Arthritis Research and Therapy 2010;12: 01-7.
3. Rosamma J, Sreeraj R, Sameera GN, Binoy JP. Association between chronic periodontitis and rheumatoid arthritis. A hospital based case control study. Rheumatol Int 2012;33:103-9
4. Miranda L A. Rheumatoid arthritis as a modifier of periodontitis. Thesis for doctoral degree (Ph.D). 2007; Karolinska Institutet, Stockholm, Sweden: 5-72
5. Loyola RJP, Martinez MRE, Abud MC, Patino MN, Seymour GI. Rheumatoid arthritis and the role of oral bacteria. J Oral Microbiol; 2010: 2;1-8
6. Torkzaban P, Hijabadi T, Basir Z, Poorolajal J. Effect of rheumatoid arthritis on periodontitis: a historical cohort study. J Periodontal Implant Sci 2012; 42:67-72.
7. Pinho MN, Oliveira RD, Novaes AB, Voltarelli JC. Relationship between Periodontitis and Rheumatoid Arthritis and the Effect of Non-Surgical Periodontal Treatment. Braz Dent Journal 2009; 20: 355-64

8. Eduardo de Paula I, Manoel B B, Carlos R Jr, Keith L K, Mirian A O. Periodontal condition in patients with rheumatoid arthritis. Braz Oral Res 2008; 22:73-7
9. Mikuls TR, Payne JB, Reinhardt RA, Thiele GM, Cannela AC, Holers VM et al. Antibody responses to Porphyromonas gingivalis (P. gingivalis) in subjects with rheumatoid arthritis and periodontitis. Int Immunopharmacol 2009 ; 9: 38-42.
10. Jeffrey M, Leslie JC, Yushun L, Richard JK, Dolphus RD, Jeffrey LE et al. Rheumatoid Arthritis and Salivary Biomarkers of Periodontal Disease, J Clin Periodontol. 2010; 37: 1068–1074.
11. William VG, Thomas. B, Janet SK, Kinney Christoph AR. Thiago M, David TW. Saliva as a diagnostic tool for periodontal disease: current state and future directions. Periodontology 2000 2009; 50: 52–64
12. 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.
13. Bartold PM, Marino V, Cantley M, Haynes DR. Effect of Porphyromonas gingivalis-induced inflammation on development of rheumatoid arthritis. J Clin Periodontol 2010; 37(5): 405–411.
14. Seneviratne CJ, Zhang CF, Samaranayake LP. Dental plaque biofilm in oral health and disease. Chin J Dent Res.2011;14:87-94
15. Marsh PD. Microbiology of dental plaque biofilms and their role in oral health and caries. Dent Clin North Am. 2010; 54 :441-54.
16. Mark IR. The influence of smoking on host responses in periodontal infections Periodontology 2000. 2007; 43: 267–77.
17. Azuma M., Fundamental mechanisms of host immune responses to infection, J Periodontol 2006; 41: 361–373.
18. Mario TJ, Janet K, Amy SK, William VG. Diagnostic Biomarkers for Oral and Periodontal Diseases. Dent Clin North A*m*. 2005; 01-21
19. Susanto H, Nesse W, Dijkstra PU, Hoedemarker E, Van Reenen YH, Aqustina D et al. Periodontal inflamed surface area and C-reactive protein as predictors of HbA1c: a study

in Indonesia. Clin Oral Invest 2012; 16:1237-42.

20. Ramamoorthy RD, Nallasamy V, Reddy R, Esther N, Martthappan Y. A review of C-reactive protein: A diagnostic indicator in periodontal medicine. J Pharm Bioallied Sci 2012; 4 (Suppl 2): S422–S426.
21. Kimmo M, Marja V, Ville V, Markku N, Timo P, Vesa R, Sirkka A. Effect of treating periodontitis on C-reactive protein levels: a pilot study. BMC Infec Dis 2002; 2:1-3
22. Chopra R, Patil SR, Kalburgi NB, Mathur S. Association between alveolar bone loss and serum C-reactive protein levels in aggressive and chronic periodontitis patients. J Indian Soc Periodontol. 2012; 16: 28–31.
23. Aubin JE, Bonnelye E. Osteoprotegerin and its ligand: a new paradigm for regulation of osteoclastogenesis and bone resorption. Osteoporos Int. 2000; 11:905-13.
24. Seymour GI, Ford PJ, Cullinan MP, Leishman S, Yamazaki K. Relationship between periodontal infections and systemic disease Journal compilation. European Society of Clinical Microbiology and Infectious Diseases 2007;(Suppl. 4): 3–10
25. Armitage GC. The complete periodontal examination. Periodontol 2000 1975; 34: 22-33

Authors Column

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