Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Host modulation therapy in periodontics - A review

Rosamma Joseph*, Amarnath V

Professor and Head, Department of Periodontics, Govt. Dental College, Kozhikode, Kerala, India.

ARTICLE HISTORY

Received: 16.03.2015

Accepted: 23.04.2015

Available online: 30.05.2015

Keywords:

Bisphosphonates,Host modulation, Non-steroidal anti-inflammatory drugs, Sub-antimicrobial dose Doxycycline.

*Corresponding author:

Email : drrosammajoseph@gmail.com
i10amarnath@gmail.com
Tel.: +91-9446070599, 9495291072

ABSTRACT

Periodontitis is one of the most prevalent chronic inflammatory diseases in humans. Periodontitis is chronic infectious condition of supporting tissues of teeth caused by sub gingival microbial colonization in susceptible hosts. Current understanding of the periodontal pathogenesis emphasizes the role of host response to pathogens in periodontal destruction. Immune inflammatory response of the host is a double edged sword which is protective by intent paradoxically resulting in tissue destruction. In periodontal disease, typical antimicrobial intervention procedures, such as scaling and root planning (SRP), will help in removing etiologic agents associated with inflammation, thereby helping to arrest periodontitis. However, such procedures do not inhibit the host mediated tissue destruction and do not offer necessary resolution of inflammation to restore tissue homeostasis. Host-modulatory pharmacotherapies are specifically target the host response mechanisms and such therapies as an adjunct to traditional antimicrobial interventions represents a new integrated approach in the management of periodontal disease. This review will cover an update on past and future host immune modulatory agents used adjunctively to treat and manage periodontal diseases.

INTRODUCTION

Periodontitis is one of the most prevalent chronic inflammatory diseases in humans. It is a chronic infectious condition of supporting tissues of teeth caused by sub gingival microbial colonization in susceptible hosts. Bacteria especially gram negative anaerobic bacteria and their products evoke an immunoinflammatory reaction in host tissue.

Periodontitis is one of the major causes of dentition loss [1]. Current data suggests that plaque biofilm and associated hostresponse are mainly involved in the pathogenesis of periodontitis. Periodontal pathogens predominantly Gram-negative, anaerobic bacteria withinbiofilm are associated with periodontal disease initiationand progression [2].The microbial challenge consisting of antigens, lipopolysaccharide and destruction is primarily by the host responses. The host responses are of mainlytwo types: anti-inflammatory or protective and proinflammatoryor destructive.

PATHOGENESIS OF PERIODONTAL DISEASE

Current understanding of the periodontal pathogenesis emphasizes the role of host response to pathogens in periodontal destruction which was proposed by page and Kornman in 1997 [3] according to them bacterial antigens and lipopolysaccharide (LPS) from invading pathogenic microorganism act on host tissue, in response host produce polymorpho nuclear neutrophils(PMNs)and antibodies against these antigens and host immune inflammatory response which leads to production of cytokines,prostanoids and matrix metallo proteinases(MMPS), these will act host connective tissue and bone along with enviormental,acquired and genetic risk factors leads to tissue break down and clinical signs of disease.

Bacteria are essential but alone will not produce the disease, Imbalance in host response dictates susceptibility along with environmental, acquired& genetic factors also play an important role in periodontal disease initiation and progression.Immune inflammatory response of the host is a double edged sword which is protective by intent paradoxically resulting in tissue destruction. In periodontal disease, typical antimicrobial intervention procedures, such as scaling and root planning (SRP), will help in removing etiologic agents associated with inflammation, thereby helping to arrest periodontitis. However, such procedures do not inhibit the host mediated tissue destruction and do not offer necessary resolution of inflammation to restore tissue homeostasis [4].The current concept in periodontal treatment emphasizes on host - microbial interactions to understand the disease process, as well as to develop novel therapeutic strategies known as host modulatory therapies [5]. *Host* can be defined as “the organism from which a parasite obtains its nourishment,” or in the transplantation of tissue, “the

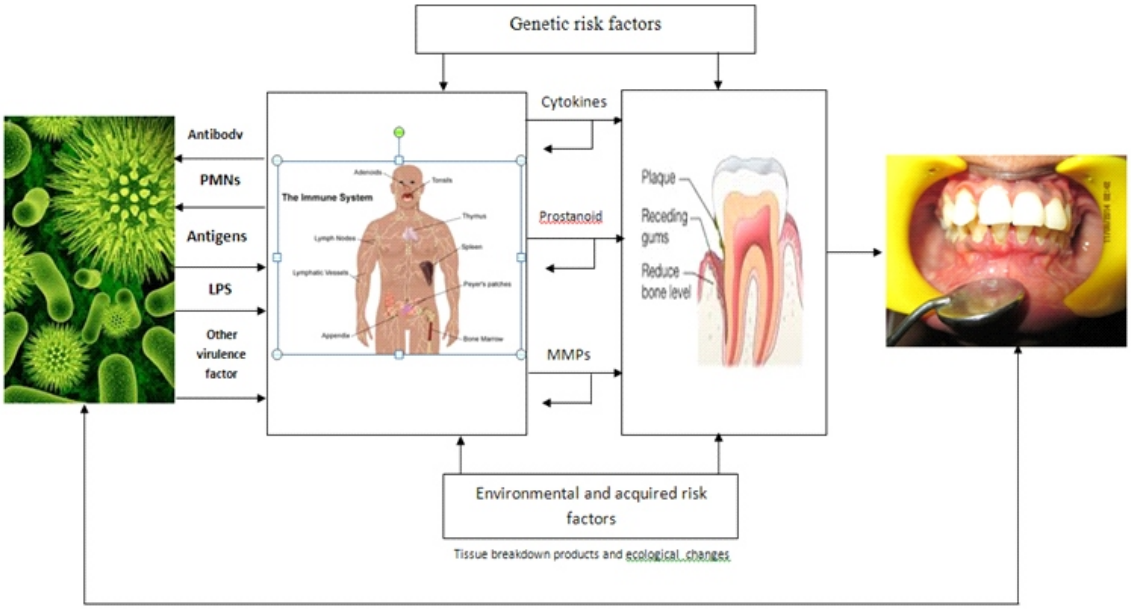

Figure 1: Idea was taken from Page and Kornman model I997

individual who receives the graft."*Modulation* is defined as "the alteration of function or status of something in response to a stimulus or an altered chemical or physical environment" (*Taber's Medical Dictionary,* 2004).

The aim of host modulation therapy (HMT) is to reduce the tissue damage and stabilize or even regenerate the periodontium by modifying or down regulatingdestructive aspects of host response and up regulating protective or regenerative responses [6]

HISTORICAL ASPECT OF HOST MODULATION

Paul Goldhaberand Max Goodson [7] began to implicate arachidonic acidmetabolites as important inflammatory mediators of the bone loss in periodontitis in the 1970s.Nyman et al [8] concluded in their study that systemic indomethacin suppressed alveolar bone loss and gingival inflammation in beagle dogs and squirrel monkeys.

Waite et al [9] reported low gingival index and shallow pocket in patients taking NSAID'S for arthritis. Williams et al[10]explained that systemic flurbiprofen decreased bone loss in beagles with naturally occurring periodontitis and theyreached in a conclusion that 50mg flurbiprofen twice daily for 24 months depressed bone loss and returned to baseline value at 6months post operative evaluation.The concept of host modulation was first introduced to dentistry by William and Golub. In 1990, Williams concluded in his study that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be efficacious in slowing the progression of periodontitis." In 1992, Golub and colleagues discussed "host modulation with tetracyclines and their chemically modified analogues." [11]

Crout et al [12] reported that subantimicrobial dose of doxycyclines (SDD) 20mg bd (periostat) along with SRP improved attachment levels in a cyclic study .Golub et al in [13] explained that 2months SDD decreased GCF MMP-8 &9 and carboxy terminal peptide.

Specific aspects of disease pathogenesis which have been investigated for modulation include regulation of immune and inflammatory responses, excessive production of matrix metalloproteinase's and arachidonic acid metabolites, and regulation of bone metabolism.The purpose of host modulatory therapy is to restore balance between on the one hand, proinflammatory mediators and destructive enzymes and on the other hand anti-inflammatory mediators and enzyme inhibitors. They can be systemically administered or locally delivered and used as adjuncts to scaling and root planning.

Advantages of hostmodulation therapies are to modulate or reduce destruction,ameliorate excessive or pathologically elevated inflammatory process, Reduce excessive levels of enzymes, cytokines and prostanoids, modulate osteoclast and osteoblast function, address many risk factors, Can also increase levels of persons own protective or anti-inflammatory mediators.

Classification of agents helping in host modulation

Systemically administered agents

1 Sub antimicrobial dose of doxycycline
2 Chemically modified tetracyclines
3 NSAIDs
4 Bisphosphonates

Locally administered Agents

1 NSAIDs
2 Enamel Matrix proteins
3 Growth factors
4 Bone morphogenic proteins

SDD-Sub antimicrobial dose of doxycycline

SDD is the only systemic host response modulator specifically indicated as adjunctive treatment for periodontitis and it is approved by USFDA[1]and UK medicines and health care products regulatory agency. It is marketed as periostat,20mg dose of doxycycline hyclate BD for 3-9 months has the ability to

down regulate MMPS

Doxycylinedownregulates MMPs by various mechanisms [14]

1 In junctional epithelium inhibition of production of epithelial derived MMPs by inhibiting cellular expression and synthesis.

2 In connective tissue - Direct inhibition of active MMPs by cation chelation Inhibition of oxidative activation of latent MMPs,down regulates the expression of key inflammatory cytokines including interleukin IL1,IL6,and tumor necrosis factor (TNF)α,as well as prostaglandin E2 (PGE2)Scavenges and inhibits production of reactive oxygen species (ROS) produced by PMNs (e.g.HOCl, which activates latent MMPs),Inhibition of MMPs and ROS protects α1 proteinase inhibitor (α1PI) thereby indirectly reducing tissue proteinase activity,Stimulates fibroblast collagen production.

3 Alveolar bone- Reduces osteoclast activity and bone resorption, blocks osteoclast MMPs, Stimulates osteoblast activity and bone formation

Indications for using SDD

Chronic periodontitis, Aggressive types of periodontitis, smokers,systemic diseases like diabetes, osteoporosis, osteopenia and genetic susceptibility.

Contraindications for using SDD

History of allergy or hypersensitivity, Pregnant and lactating women, Children under 12yrs of age, May reduce the effectiveness of oral contraceptives.

SDD may not used as monotherapy. It is used as an adjunct to SRP at a dose of 20 mg twice daily for 3 months and up to a maximum of 9 months[15].Three month prescription fits well with the typical maintenance recall of 3 months.SDD therapy is commenced at the start of initial periodontal therapy and continues for three months until the first reevaluation or maintenance appointment. Atmaintenance appointment the need for further prescription of SDD may be assessedfor patients demonstrating good treatment response with significant reduction in probing depths further SDD may not be necessary. Sites with persisting or progressing pockets may require additional instrumentation, and prescription of SDD may be extended for an additional 3 months.

Doxycycline at antibiotic dose is associated with adverse effects, including photosensitivity, hypersensitivity reactions, nausea, vomiting and esophagealirritation. But clinical trials of SDD (20mg dose), it was reported that the drug was well tolerated.Benefits of Therapy includes down regulation of MMP activity in inflamed periodontal tissues, Improvement in clinical parameters when combining SDD with SRP.Reduction in probing depths and gain in attachment that may observed after SRP plus SDD, the quality of periodontal tissue may also tend to improve after treatment with SDD.

Chemically Modified Tetracyclines

Chemically modified tetracyclines (CMTs) are one of the most promising groups of potential HMTS,devoid of antibacterial activity due to removal of dimethyl amino group from C-4position of A ring, but it retain hostmodulatory, anticollagenolytic effects. These agents act as potent inhibitors of proinflammatory mediators and can increase levels of anti-inflammatory mediators such as IL-10.

In 1985, CMTs had been discovered to have anticollagenolytic activity and was proposed as a host-modulating agent for periodontal treatment [16].10 different CMTS have been identified as CMTS 1-10.

Chemically modified tetracycline's (CMTs) [16] act by Inhibition of production of epithelial derived MMPs by inhibiting cellular expression and synthesis, Inhibits or chelates the calcium ions that MMPs requires for their action. It inhibit already active MMPs, Scavenges reactive oxygen species, Modulates the osteoclast functions. Othereffects of CMTS include inhibition of tumor cell invasion, attenuation of intimal thickening after arterial injury.

Inhibition of arachidonic acid metabolite:

Arachidonic acid can be metabolized via cyclooxgenase (COX) or lipooxygenase (LOX) pathways. The final products of the COX pathway include prostaglandins, prostacyclin, and thromboxane. Elevated levels of PGE2 and other arachidonic acid metabolites have been reported in gingival crevicular fluid and periodontal tissues in patients exhibiting gingivitis and periodontitis, [16]. Mean crevicular PGE2 concentrations are also significantly elevated in patients who exhibit disease progression compared to periodontally stable individuals. One proposed approach to modulate the host response is inhibition of enzymes responsible for the release of these destructive products [16].

Nonsteroidal Anti inflammatory Drugs (NSAIDS)

Gram negative bacteria produce LPS act on neutrophils, Macrophages and fibroblast and produce PGE2.NSAIDS inhibits these PGE2 production, Reducing inflammation and inhibiting osteoclast activity in periodontal tissue. PGE2 Upregulates bone resorption by osteoclast. Levels of PGE2 have shown to be elevated in patients with periodontal disease compared with healthy patients. PGE2 also inhibits fibroblast function and has inhibitory and modulatory effect on immune response.Studies have shown that systemic NSAIDS such as Indomethacin, Flurbiprofen and Naproxen administered daily for up to3yrs significantly slowed the rate of alveolar bone loss.Daily administration for extended periods is necessary for periodontal benefits.

Disadvantages of NSAIDS includes gastrointestinal (GI) problems,Hemorrage, Renal and hepatic impairment,Periodontal benefits of taking long term NSAIDS are lost when patients stop taking the drugs, with a return to or even an acceleration of the rate of bone loss seen before NSAID therapy, often referred to as a "rebound effect".

Cyclooxygenase converts arachidonic acid to prostaglandins, Inhibition of COX-2 by selective COX-2 inhibitors results in reduction of inflammation without the side effects typically observed after long termtherapy.COX-2 inhibitors later identified to be associated with significant life- threatening adverse effect. So NSAIDS including selective COX-2 inhibitors are presently not indicated as adjunctive HMTS in the treatment of periodontal disease.

Bisphosphonates

The bisphosphonates are bone-seeking agents that inhibitbone resorption by disrupting osteoclast activity [14]

CLASSIFICATION

First generation (alkyl side chains)Etidronate

Second generation (amino terminal group) Alendronate &pamidronate

Third generation (cyclic side chains)Risedronate

Mechanism of action of bisphosphonates as host modulation agent[9]

Bisphosphonates acts on osteoclast function at Tissue,Cellular and molecular levels

1 Tissue level: Decrease bone turnover due to decreased bone resorption, Decreased number of bone multicellular units, Net positive whole body bone balance

2 Cellur level: Decreased osteoclast recruitment, Increased osteoclast apoptosis,Decreased osteoclast adhesion, Increased osteoblast differentiation and number

3 Molecular level: Inhibit mevalonate pathway,Decreased post translational phenylation of GTP binding proteins

Rocha et al [17] used oral route of alendronate as host modulating agent and found that there is decreased alveolar bone resorption, decreased tooth mobility and decreased clinical parameters.Pradeep AR et al [18] used Alendronate as local drug delivery as 1% gel and found that there isincrease percentage of bone fill, decreased probing depth and clinical attachment level.Unwantedside effects of Bisphosphonates are Inhibition of bone calcification, Induce changes in WBC count, Also report of avascular necrosis of jaws following bisphosphonate therapy, with resultant risk of bone necrosis following extraction. The necrosis was in patients administered IV bisphosphonates as HMT agent. Atpresent no bisphosphonate drugs that are approved and indicated for treatment of periodontal disease.

Enamel MatixProteins,Growth factors and bone morphogenetic proteins

The locally applied HMTs currently approved by the FDA for adjunctive use during surgery are enamel matrix proteins (Emdogain), Recombinant human platelet-derived growth factor BB(GEM21S) and BMP-2(Infuse).

Emerging host modulatory Therapies.

One of the most promising groups of potential HMTS is the *chemically modified tetracyclines* (CMTs). *Anticytokine drugs* are developed for the management of rheumatoid arthritis.Cytokines such as TNF-α have been targeted by TNF-α antagonists (e.g., Infliximab, Etanercept), which have been shown to be effective in treating rheumatoid arthritis.Drugs designed to increase the levels of anti-inflammatory or protective mediators, such as IL-1ra.Combination of anti-inflammatory drugs with resolving agents tested in human clinical trials may provide evidence to support a brand new host modulation therapy for the management of periodontal diseases.

Host modulation factors in systemic disorders.

Host modulators used to manage periodontal disease, such as MMP, cytokine and prostanoid inhibitors, may have additional beneficial effects on systemic diseases that have been linked to periodontal disease such as CVD and diabetes.

Golub et al [19] suggested that tetracycline's could reduce the incidence of acute myocardial infarction by blocking colllagenase and stabilizing the collagen cap on the atherosclerotic arterial plaques.HMT may also directly aid in the treatment and prevention of CVD and diabetic complications.

DISCUSSION

Current understanding of the periodontal pathogenesis emphasizes the role of host response to pathogens in periodontal destruction. Bacterial antigens and LPS from invading pathogenic microorganism act on host tissue in response host produce PMNs and antibodies against these antigens and host immune inflammatory response which leads to production of cytokines prostanoids and MMPS, these will act host connective tissue and bone along with enviormental, acquired and genetic risk factors leads to tissue break down and clinical signs of disease.

In periodontal disease, typical antimicrobial intervention procedures, such as scaling and root planning (SRP), will help in removing etiologic agents associated with inflammation, thereby helping to arrest periodontitis. However, such procedures do not inhibit the host mediated tissue destruction and do not offer necessary resolution of inflammation to restore tissue homeostasis [11].

The aim of host modulation therapy (HMT) is to reduce the tissue damage and stabilize or even regenerate the periodontium by modifying or down regulating destructive aspects of host response and up regulating protective or regenerative responses [6].

HMT is gaining interest among periodontists as an additional therapeutic option for treatment of periodontal diseases.The conventional treatment only focus on removal of plaque biofilm by mechanical therapy based on nonspecific plaque hypothesis whereas modern treatment strategy depends on successful implementation of mechanical therapy, modification of risk factors and host modulation therapy[2]. It is evident that mechanical therapy remains the primary focus for successful treatment whereas HMT is only recommended as an adjunct to conventional therapy for better clinical outcome. Also the modification of riskfactors either modifiable (e.g. smoking, uncontrolled diabetes) or non-modifiable (e.g. genetics, gender etc) plays a pro-vital role in successful treatment. There are many clinical situations in which desired clinical results cannot be achieved with mechanical therapy alone e.g. presence of risk factors, presence of systemic disease etc, therefore, adjunct use of HMT is indicated. HMT plays an important role in down regulation of immune and inflammatory mediators mainly by inhibiting MMPs, decreasing arachidonic acid metabolites and regulating osteoclast activity. With the current available research data SDD is an effective adjunct therapy when used in dosage of 20 mg twice daily for minimum duration of 3-9 months in cases of moderate to severe chronic periodontitis. FDA has only approved SDD to in dosageof 20 mg B.I.D as an adjunct SRP for the treatment ofchronic periodontitis. Benefits of Therapy includes down regulation of MMP activity in inflamed periodontal tissues, Improvement in clinical parameters when combining SDD with SRP.Reduction in probing depths and gain in attachment that may observed after SRP plus SDD, the quality of periodontal tissue may also tend to improve after treatment with SDD.Golub et al [13] showed that a 2 month regimen of SDD significantly decreased both the level of bone type collagen break down products and MMP-8,MMP-13 enzyme levels in chronic periodontissubjects.Needleman et al in 2007[20]a meta-analysis of randomized clinical trials of SDDused as an adjunct to SRP

revealed a benefit when using SDD in smokers with periodontitis.

CONCLUSION

Certain patients possess nonmicrobial risk factors which are difficult to reduce or eliminate (smoking,diabetes) or are beyond the clinicians ability to control(genetic predisposition). In these instances and for specific group of periodontal disease susceptible individuals, the use of HMT in conjunction with antibiofilm may prove to be advantageous. Practitioners will need to determine the utility of HMT therapies as they emerge based on the specific needs of each individual patient.

REFERENCES

1. Giannobile WV. Host-response therapeutics for periodontal diseases. *J Periodontol*2008; 79:1592-600.
2. Preshaw PM, Seymour RA, Heasman PA. Current concepts in periodontal pathogenesis. *Dent Update* 2004; 31:570-8.
3. Page, Roy C, & Kornman, Kenneth S. (1997). The pathogenesis of human periodontitis: an introduction. *Periodontology 2000, 14*(1), 9-11.
4. Van Dyke TE. The management of inflammation in periodontal .*J Periodontol*2008; 79:1601-8.
5. Liljana Bogdanovska, Silvana Kukeska, Therapeutic strategies in the treatment of periodontitis *Macedonian pharmaceutical bulletin* 2012, 58 (1, 2) 3 - 14
6. Shinwari, Muhammad Saad, Tanwir, Farzeen, Hyder, Pakiza Raza, & Bin, Saeed MH. Host modulation therapeutics in periodontics: role as an adjunctive periodontal therapy. *Journal of the College of Physicians and Surgeons--Pakistan: JCPSP,* 2014. *24*(9), 676-684.
7. Williams, Ray C. Non-steroidal anti-inflammatory drugs for altering periodontal bone loss. *Journal of dental research,* 1999: *78*(2), 638-642.
8. Nuki, K, Soskolne, WA, Raisz, LG, Kornman, KS, &Alander, C. (1981). Bone resorbing activity of gingiva from beagle dogs following metronidazole and indomethacin therapy. *Journal of periodontal research, 16*(2), 205-212.
9. Howell, T Howard, & Williams, Ray C. Nonsteroidal antiinflammatory drugs as inhibitors of periodontal disease progression. *Critical Reviews in Oral Biology & Medicine,*1993: *4*(2), 177-196.
10. Jeffcoat, MK, Williams, RC, Reddy, MS, English, R, &Goldhaber, P. (1988). Flurbiprofen treatment of human periodontitis: effect on alveolar bone height and metabolism. *Journal of periodontal research, 23*(6), 381-385.
11. Newman, Michael G, Takei, Henry, Klokkevold, Perry R, & Carranza, Fermin A. 2011.p.705*Carranza's clinical periodontology*: Elsevier health sciences.
12. Thomas, JG, Metheny, RJ, Karakiozis, JM, Wetzel, JM, &Crout, RJ. (1998). Long-term sub-antimicrobial doxycycline (Periostat®) as adjunctive management in adult periodontitis: Effects on subgingival bacterial population dynamics. *Advances in dental research, 12*(1), 32-39.
13. Golub, LM, Lee, H-M, Ryan, ME, Giannobile, WV, Payne, J, &Sorsa, Timo. (1998). Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Advances in dental research, 12*(1), 12-26.
14. Kornman, Kenneth S. Host modulation as a therapeutic strategy in the treatment of periodontal disease. *Clinical infectious diseases,* 1999, *28*(3), 520-526.
15. yan, Maria Emanuel. (2005). Nonsurgical approaches for the treatment of periodontal diseases. *Dental clinics of North America, 49*(3), 611-636.
16. Anarthe, Raju, Mani, Ameet, &Marawar, PP. Host Modulatory Therapy: A Novel Approach in Periodontal Therapy. *IOSR Journal Of Pharmacy 2013(p)-ISSN: 2319-4219*
17. Jeffcoat, Marjorie K. (2006). Safety of oral bisphosphonates: controlled studies on alveolar bone. *International Journal of Oral and Maxillofacial Implants, 21*(3), 349.
18. Sharma, Anuj, & Pradeep, AR. (2012). Clinical efficacy of 1% alendronate gel as a local drug delivery system in the treatment of chronic periodontitis: a randomized, controlled clinical trial. *Journal of periodontology, 83*(1), 11-18.
19. Villarreal, Francisco J, Griffin, Michael, Omens, Jeffrey, Dillmann, Wolfgang, Nguyen, Judy, &Covell, James. (2003). Early short-term treatment with doxycycline modulates postinfarction left ventricular remodeling. *Circulation, 108*(12), 1487-1492.
20. Needleman, Ian, Suvan, Jean, Gilthorpe, Mark S, Tucker, Richard, St George, Geoff, Giannobile, William, Jarvis, Martin. . A randomized□controlled trial of low-dose doxycycline for periodontitis in smokers. *Journal of clinical periodontology,* 2007, *34*(4), 325-333.