

# The Systemic Host Modulation Therapy of Periodontal Diseases

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## ABSTRACT

**Background:** The systemic host modulation therapy is new approach in treatment of periodontal diseases.

**Materials and methods:** The target of this treatment is the host response to microbial infection because at present time, it is well known that most of damage found in periodontal diseases cause by the inflammatory-immune response to periodontal infections. Sub-antimicrobial-dose Doxycycline (SDD) is a 20-mg dose of Doxycycline (Periostat) that is approved and indicated as an adjunct to scaling and root planning (SRP) in the treatment of chronic periodontitis.

**Results:** At present, SDD (Periostat) is the only systemically administered agent that is approved by the U.S. Food and Drug Administration (FDA) and accepted by the American Dental Association (ADA).

**Keywords:** Periostat. (J Bagh Coll Dentistry 2016; 28(2):79-83).

## INTRODUCTION

Host modulation is a relatively new term that has been incorporated into our dental jargon, but it has not been well defined. Host can be defined as “the organism from which a parasite obtains its nourishment,” or in the transplantation of tissue, “the 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).

In diseases of the periodontium that are initiated by bacteria, the “host” clearly is the individual who harbors these pathogens; however, it was not clear for many years whether it was possible to modulate the host response to these pathogens and other stimuli leading to the breakdown of the attachment apparatus. Host modulation with chemotherapeutic agents or drugs is the latest adjunctive therapeutic option for the management of periodontal diseases. The concept of host modulation is fairly new to the field of dentistry but is universally understood by most physicians who routinely apply the principles of host modulation to the management of a number of chronic progressive disorders such as arthritis and osteoporosis.

Until relatively recently, treatment options for periodontal disease have focused solely on reducing the bacterial challenge by nonsurgical therapy, surgery, and systemic or local antimicrobial therapy. Although bacteria are necessary for disease initiation, they are not sufficient to cause disease progression unless there is an associated inflammatory response within a susceptible host <sup>(1)</sup>.

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The development of SDD as an HMT, driven by research into the pathogenesis of periodontal disease, is a great example of how translational research can lead to new treatments. By better understanding the biochemical processes that are important in periodontal disease, a pharmacologic principle (Doxycycline downregulates MMP activity) has been used in the development of a new drug treatment. Data presented from research studies show the clinical benefits of adjunctive SDD, and the science behind SDD has been transferred into clinical practice. In other words, dentists now have the opportunity to use SDD for patient care, with the aim being to enhance the treatment response to conventional therapy.

## Agents used for systemic host modulation therapy

The potential adjunctive therapeutic agents that can reduce the destruction of periodontium in periodontal diseases are the non-steroidal anti-inflammatory drugs, bisphosphonates and subantimicrobial dose of doxycycline (figure 2).

### 1) Non-steroidal anti-inflammatory drugs (NSAIDs)

The NSAIDs inhibit the formation of prostaglandins, including PGE<sub>2</sub>, which is produced by neutrophils, macrophages, fibroblasts and gingival epithelial cells in response to the presence of lipopolysaccharide (LPS), a component of the cell wall of gram negative bacteria. PGE<sub>2</sub> has been extensively studied in periodontal disease because it upregulates bone resorption by osteoclasts <sup>(3)</sup>. However, NSAIDs have some serious disadvantages when considered for use as a HMT for periodontitis. Daily administration for extended periods is necessary for periodontal benefits to become apparent, and NSAIDs are associated with significant side effects, including gastrointestinal problems,

hemorrhage<sup>(4)</sup>, and renal and hepatic impairment. Furthermore, research shows that the 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”<sup>(5)</sup>. For these reasons, the long-term use of NSAIDs as an adjunctive treatment for periodontitis has never really developed beyond research studies.

**2) Bisphosphonates**

Bisphosphonates are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases. They are the most commonly prescribed drugs used to treat osteoporosis.

**Adverse effects**

Oral bisphosphonates can cause upset stomach and inflammation and erosions of the esophagus, which is the main problem of oral N -containing preparations. Bisphosphonates, when administered intravenously for the treatment of cancer, have been associated with osteonecrosis of the jaw (ONJ)<sup>(6)</sup>.

A study had reported bisphosphonate use (specifically zoledronate and alendronate) as a risk factor for atrial fibrillation in women<sup>(7)</sup>. In Europe and North America, the incidence of oesophageal cancer at age 60–79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates<sup>(8)</sup>.

**3) Sub-Antimicrobial-Dose Doxycycline(SDD)**

Sub-antimicrobial-dose doxycycline (SDD) is a 20-mg dose of doxycycline (Periostat) that is approved and indicated as an adjunct to scaling and root planning (SRP) in the treatment of chronic periodontitis. It is taken twice daily for 3 months, up to a maximum of 9 months of continuous dosing. The 20-mg dose exerts its therapeutic effect by enzyme, cytokine, and osteoclast inhibition rather than by any antibiotic effect. At present, SDD (Periostat) is the only systemically administered HMT specifically indicated for the treatment of chronic periodontitis that is approved by the U.S. Food and Drug Administration (FDA) and accepted by the American Dental Association (ADA).

**A-Mechanisms of Action**

In addition to its antibiotic properties, Doxycycline (as well as the other members of the tetracycline family) has the ability to downregulate MMPs, a family of zinc-dependent

enzymes that are capable of degrading extracellular matrix molecules, including collagen (table 1)<sup>(9)</sup>. MMPs are secreted by the major cell types in the periodontal tissues (fibroblasts, keratinocytes, macrophages, polymorphonuclear leukocytes (PMNs), endothelial cells) and play a key role in periodontitis. Excessive quantities of MMPs are released in inflamed periodontal tissues, resulting in breakdown of the connective tissue matrix. The predominant MMPs in periodontitis, particularly MMP-8 and MMP-9, derive from PMNs and are extremely effective in degrading type I collagen, the most abundant collagen type in gingiva and periodontal ligament. The release of large quantities of MMPs in the periodontium leads to significant anatomic disruption and breakdown of the connective tissues, contributing to the clinical signs of periodontitis<sup>(10)</sup>.

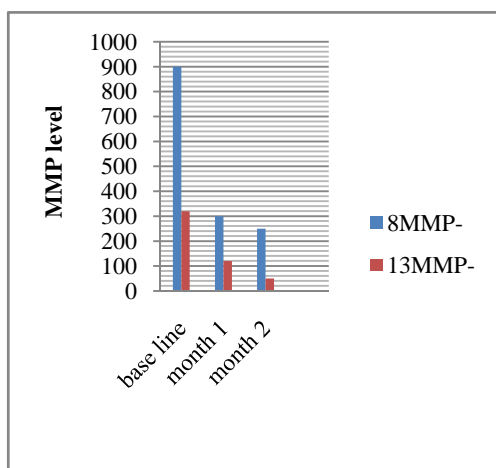
**Table1: The mechanisms by which Doxycycline inhibits connective tissue breakdown. Downregulation of destructive events occurring in the periodontal tissues by Doxycycline results from modulation of a variety of different proinflammatory pathways<sup>(11)</sup>.**

-Inhibition of production of epithelial driven MMPS.
-Direct inhibition of active MMPS by cation chelation
-Inhibition of oxidative activation of latent MMPS.
-Down regulates expression of key inflammatory cytokines including interleukin 1(IL1), interleukin6(IL6), and tumour necrosis factor alpha as well as PGE2.
-Scavenge and inhibits production of reactive oxygen species(ROS) produced by PMNs(e.g,HOCl which activate latent MMPs).
-Stimulate fibroblast collagen production.
-Reduce osteoclast activity.
-Block osteoclast MMPs.
-Stimulate osteoblast activity.

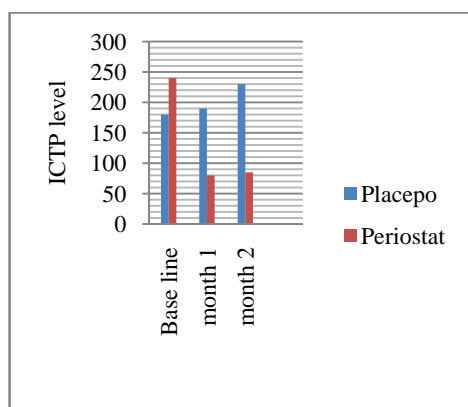
**B-Clinical research data on distinct patient populations**

In a study, 3-month regimen of SDD produced a prolonged drug effect without a rebound in collagenase levels to baseline during the no-treatment phase of the study<sup>(12)</sup>. The mean levels of gingival crevicular fluid (GCF) collagenase were significantly reduced (47.3% from baseline levels) in the SDD group versus the placebo group, who received scaling and prophylaxis alone (29.1% reduction from baseline levels). Accompanying these reductions in collagenase levels were gains in the relative attachment levels in the SDD group. Continuous drug therapy over

several months appears to be necessary for maintaining collagenase levels near normal over prolonged periods. However, it is reasonable to speculate that levels of these MMPs will eventually increase again in the more susceptible patients, and those individuals having the most risk factors and the greatest microbial challenge will require more frequent HMT than other patients.



(MMP levels measure by densitometric units).



(GCF carboxyl terminal peptide fragment of type-1 collagen measure by pg ICTP/SITE).

**Figure 1: Effect of sub-antimicrobial-dose Doxycycline (SDD) on gingival crevicular fluid (GCF) collagenase (MMP-8, MMP-13) and ICTP.**

A two-month regimen of SDD significantly decreased levels of matrix metalloproteinases (MMP-8 and MMP-13, neutrophil and bone-type collagenases, respectively) and ICTP compared with placebo in GCF samples of chronic periodontitis patients<sup>(13)</sup>.

**C-High risk Patients**

A meta-analysis of randomized clinical trial of SDD used as an adjunct to SRP revealed a benefit when using SDD in smokers with periodontitis<sup>(14)</sup>. The responses of the smokers who received SDD and the nonsmokers who received placebo were intermediate to the two extremes and were broadly identical. Improving on the clinical measurements of Periodontitis<sup>(15)</sup>; SDD significantly reduced the progression of periodontal attachment loss and the severity of gingival inflammation and alveolar bone loss in postmenopausal osteopenic women.

**D-Combining SDD with periodontal surgery or local delivery systems**

However, emerging data in which SDD was used as an adjunct to access flap surgery in 24 patients revealed better probing depth reductions in surgically treated sites greater than 6mm compared with surgically treated sites in patients given placebo<sup>(16)</sup>. Furthermore, the SDD group demonstrated greater reductions in ICTP (carboxy-terminal peptide, a breakdown product of collagen) than the placebo group, indicating that collagenolytic activity was reduced in the patients taking SDD.

Preliminary results from a 6-months, 180-patient clinical trial designed to evaluate the safety and efficacy of SDD combined with a locally applied antimicrobial (Doxycycline hyclate [Atridox]) and SRP versus SRP alone demonstrated that patients receiving the combination of treatments experienced more than a 2-mm improvement in mean attachment gains and probing depth reductions ( $P < 0.0001$ ) compared with SRP alone<sup>(17)</sup>.

**E-Susceptible patient populations**

Much interest has focused on genetic susceptibility to periodontal disease, particularly whether a specific variation in the genes that regulate the cytokine IL-1 confers increased susceptibility to disease. This polymorphism is known as the periodontitis-associated genotype (PAG), when the genotype-positive patients received SDD and specific biochemical markers were monitored at 2 and 4 months, a significant decrease (50% to 61%) in the IL-1 $\beta$  and MMP-9 levels was noted after treatment with SDD. Correspondingly, gains in clinical attachment level and reduced probing depths were also observed<sup>(18)</sup>.

### F-Side effects

Doxycycline at antibiotic doses ( $\geq 100$  mg) is associated with adverse effects, including photosensitivity, hypersensitivity reactions, nausea, vomiting, and esophageal irritation. However, in the clinical trials of SDD (20-mg dose), it was reported that the drug was well tolerated, and the profile of unwanted effects was virtually identical in the SDD and placebo groups<sup>(19)</sup>. No evidence of developing antibiotic resistance of the microflora after 2 years of continuous use<sup>(20)</sup>.

### I-Sequencing prescription with periodontal treatment

The SDD is indicated as an adjunct to mechanical periodontal therapy and should not be used as a stand-alone or monotherapy. SDD should be prescribed to coincide with the first round of SRP and is prescribed for 3 months, up to a maximum of 9 to 24 months of continuous dosing depending on the patient risk<sup>(21)</sup>.

### **Host modulation factors in systemic disorders:-**

In fact, it was suggested that Tetracyclines could reduce the incidence of acute myocardial infarction<sup>(22)</sup> by blocking collagenase and stabilizing the collagen cap on the atheroscleromatous arterial plaques. Other study have shown that SDD reduces systemic inflammatory biomarkers in cardiovascular diseased patients<sup>(23)</sup> and SDD decreases glycosylated hemoglobin (HbA1c) assay in patients who are taking normally prescribed hypoglycemic agents.

### **CONCLUSIONS**

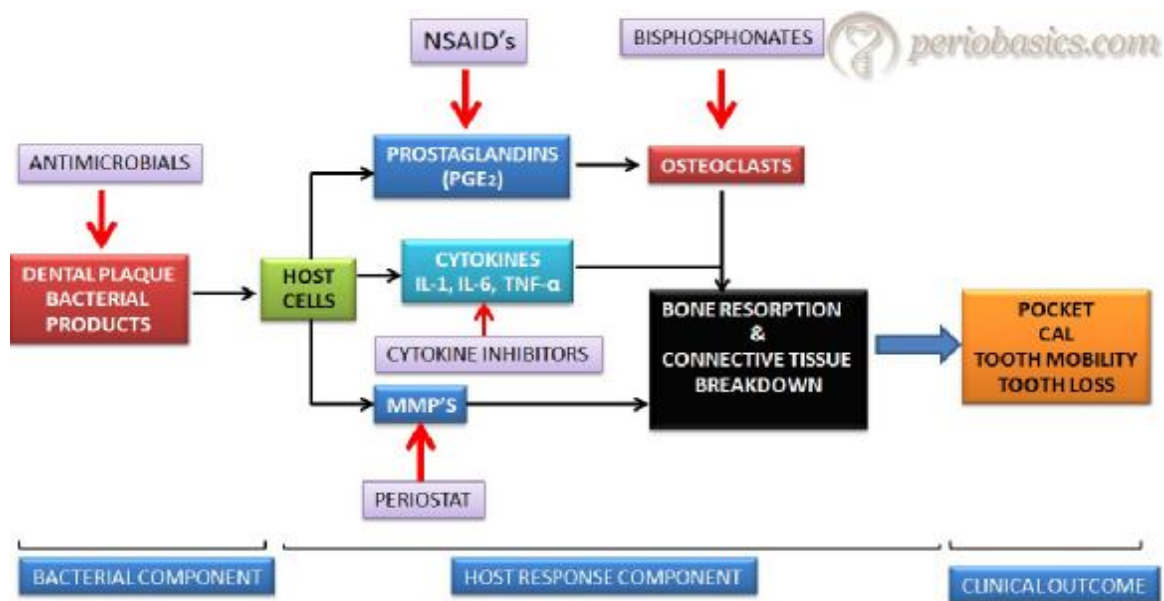
SDD is the only systemically administered HMT currently approved and indicated as an adjunct to SRP for treating periodontitis. Clinical trials have demonstrated a clear treatment benefit when using SDD versus SRP alone. SDD should be used as part of a comprehensive treatment strategy that includes antibacterial treatments (SRP, plaque control, oral hygiene instruction, local antimicrobials, and periodontal surgery), host response modulation (SDD), and assessment and management of periodontal risk factors. In the future, a range of HMTs targeting different aspects of the destructive cascade of breakdown events in the periodontal tissues are likely to be developed as adjunctive treatments for periodontitis. The further development of these agents will permit dentists to treat specific aspects of the underlying biochemical basis for periodontal disease.

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**Figure 2: Potential adjunctive therapeutic approaches .Possible adjunctive therapies and points of intervention in the treatment of periodontitis are presented related to the pathologic cascade of events . CAL , Clinical attachment loss<sup>(2)</sup>**