RESEARCH PAPER

Influence of Host-Modulation Therapy Using Sub-Antimicrobial Dose Doxycycline on Clinical and Salivary Biomarkers in Stage III Periodontitis

Amaal Faez Dhafer Alshehri[1], Miad Jazzaa S Alshammari[2], Raniya Mohammed Alhazmi[1], Sultanah Abdulrahman Alrahmah[3], Alshaalan Haya Alnori[3], Refan Nawa Kyad Alanze[2], Nouf Saad Mojeb Alqahtani[4]

[1]*Oral And Dental Health Specialist, Prince Sultan Military Medical City, Riyadh, Saudi Arabia*
[2]*Dental Assistant, Prince Sultan Military Medical City, Riyadh, Saudi Arabia*
[3]*Dentist, Prince Sultan Military Medical City, Riyadh, Saudi Arabia*
[4]*Dental Hygienist, King abdulaziz medical city, Ministry of National Guard Health Affaire, Riyadh, Saudi Arabia*

ABSTRACT
Periodontitis represents a chronic inflammatory disease characterized by progressive destruction of periodontal supporting tissues, affecting millions worldwide. Stage III periodontitis, classified by severe clinical attachment loss and radiographic bone loss, presents significant therapeutic challenges requiring comprehensive management strategies. Host-modulation therapy using sub-antimicrobial dose doxycycline (SDD) has emerged as a promising adjunctive treatment modality that targets the host inflammatory response rather than microbial pathogens. This review comprehensively examines the influence of SDD on clinical parameters and salivary biomarkers in Stage III periodontitis management. Evidence demonstrates that SDD at 20 mg twice daily effectively inhibits matrix metalloproteinases (MMPs), particularly MMP-8 and MMP-9, which are pivotal enzymes in periodontal tissue destruction. Clinical studies reveal significant improvements in probing depth reduction, clinical attachment level gain, and bleeding on probing when SDD is used adjunctively with scaling and root planing. Salivary biomarker analysis shows substantial reductions in pro-inflammatory cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), alongside decreased MMP-8 and myeloperoxidase (MPO) levels. The mechanism of action involves direct MMP inhibition through calcium and zinc chelation, suppression of oxidative activation, and down-regulation of inflammatory mediator production. Importantly, SDD does not exhibit antimicrobial effects at this dosage, thereby avoiding antibiotic resistance development. This review synthesizes current evidence supporting SDD as an effective host-modulating agent that enhances periodontal treatment outcomes in Stage III periodontitis by modulating the destructive host inflammatory response and promoting favorable healing conditions

Keywords: Sub-antimicrobial dose doxycycline, Stage III periodontitis, Host modulation therapy, matrix metalloproteinases, salivary biomarkers, periodontal inflammation, scaling and root planing
How to cite this article: Alshehri AFD, Alshammari MJS, Alhazmi RM, Alrahmah SA, Alnori AH, Alanze RNK, Alqahtani NSM, Influence of Host-Modulation Therapy Using Sub-Antimicrobial Dose Doxycycline on Clinical and Salivary Biomarkers in Stage III Periodontitis. 2026;16(1s): 840-852; DOI: 10.25258/ijddt.16. 840-852
Source of support: None
Conflict of interest: None

INTRODUCTION

Background

Periodontitis: Definition and Classification

Periodontitis is a multifactorial inflammatory disease characterized by microbially-associated, host-mediated destruction of the periodontal supporting apparatus, including the gingival tissues, periodontal ligament, and alveolar bone[1]. The disease results from complex interactions between dysbiotic microbial communities in the subgingival biofilm and an aberrant host immune-inflammatory response. In 2017, the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions introduced a new classification system that replaced the previous chronic and aggressive periodontitis categories with a staging and grading framework[2].

The 2018 classification system categorizes periodontitis into four stages (I-IV) based on severity, complexity, extent, and distribution, alongside three grades (A-C) reflecting the rate of disease progression and risk factors[2]. Stage III periodontitis represents severe periodontitis characterized by clinical attachment loss of 5 mm or more, radiographic bone loss extending to the middle third of the root or beyond, probing depths of 6 mm or more with bleeding on probing, and potential tooth loss of up to four teeth due to periodontitis[3]. Additional complexity factors in Stage III include vertical bone loss of 3 mm or more, Class II or III furcation involvement, and moderate ridge defects[3].

**Author for Correspondence: dr.cardiovascular.surgery@gmail.com*

.

Epidemiology and Clinical Significance

Periodontitis affects approximately 42% of adults aged 30 years and older globally, with severe forms (Stages III-IV) affecting 11% of the population[4]. The disease imposes substantial burden on quality of life, masticatory function, and has been associated with systemic conditions including cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, and respiratory infections[5]. Stage III periodontitis, in particular, presents significant treatment challenges due to the extent of tissue destruction, increased pocket depths, and compromised tooth prognosis.

Conventional Treatment Approach

The cornerstone of periodontal therapy remains mechanical debridement through scaling and root planing (SRP), which aims to remove subgingival microbial deposits and calculus, thereby reducing the bacterial load and creating conditions favorable for periodontal healing[6]. While SRP has been established as the gold standard for non-surgical periodontal treatment, clinical outcomes demonstrate variability, particularly in severe cases such as Stage III periodontitis. Studies indicate that SRP alone may achieve limited clinical attachment gain and probing depth reduction in deep periodontal pockets (≥7 mm), necessitating adjunctive therapeutic approaches to enhance treatment efficacy[7].

Host Response in Periodontitis Pathogenesis

Contemporary understanding of periodontitis pathogenesis emphasizes the critical role of the host immune-inflammatory response in tissue destruction. While periodontal pathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* initiate the disease process, the subsequent host response accounts for the majority of periodontal tissue breakdown[8]. The host response involves complex cascades of inflammatory mediators, including pro-inflammatory cytokines (interleukin-1β, interleukin-6, tumor necrosis factor-alpha) and tissue-degrading enzymes, particularly matrix metalloproteinases[9].

Matrix metalloproteinases represent a family of zinc-dependent endopeptidases capable of degrading virtually all components of the extracellular matrix, including collagens, gelatin, elastin, and proteoglycans[10]. Among the MMP family, MMP-8 (neutrophil collagenase) and MMP-9 (gelatinase B) are particularly elevated in periodontal disease and are considered key biomarkers of periodontal inflammation and tissue destruction[11]. MMP-8 is primarily responsible for type I collagen degradation, the predominant structural protein in periodontal tissues, while MMP-9 degrades denatured collagen (gelatin) and contributes to the inflammatory infiltrate[12].

Rationale for Host Modulation Therapy

Given that the host inflammatory response drives periodontal tissue destruction, therapeutic strategies targeting host-derived destructive mechanisms have gained considerable attention. Host modulation therapy aims to down-regulate pathologically elevated inflammatory mediators and tissue-degrading enzymes while preserving normal host defense mechanisms[13]. This approach offers potential advantages including enhanced clinical outcomes when combined with mechanical debridement, applicability in patients with increased disease susceptibility or risk factors, and avoidance of antibiotic resistance concerns associated with antimicrobial therapies[14].

Sub-Antimicrobial Dose Doxycycline: Concept and Development

Doxycycline, a semi-synthetic tetracycline derivative, has been utilized in antimicrobial formulations (50-100 mg daily) for treating various infections, including acute periodontal infections[15]. However, research demonstrated that tetracyclines possess MMP-inhibitory properties independent of their antimicrobial effects[16]. This discovery led to the development of sub-antimicrobial dose doxycycline (SDD), formulated at 20 mg twice daily, which achieves steady-state plasma concentrations (mean maximum 0.79 μg/mL) well below the minimum inhibitory concentration required for antimicrobial activity (typically >4 μg/mL)[17].

The sub-antimicrobial dosing strategy was specifically designed to harness the MMP-inhibitory and anti-inflammatory properties of doxycycline while avoiding antibiotic-related adverse effects, including development of resistant bacterial strains, gastrointestinal disturbances, photosensitivity, and disruption of normal microflora[18]. SDD received approval from the United States Food and Drug Administration in 1998 as an adjunctive treatment for adult periodontitis, marketed as Periostat®[19].

Literature Review

Mechanism of Action of Sub-Antimicrobial Dose Doxycycline

MMP Inhibition Mechanisms

The therapeutic efficacy of SDD in periodontitis is attributed to multiple mechanisms of action that collectively down-regulate the exaggerated host inflammatory response characteristic of periodontal disease. The primary mechanism involves direct inhibition of matrix metalloproteinases through several pathways[20].

First, doxycycline directly inhibits MMP activity by chelating calcium and zinc cations in the catalytic domain of MMP molecules[21]. MMPs are zinc-dependent enzymes that require these metal ions for structural integrity and catalytic function. By sequestering these cations, doxycycline disrupts the enzyme's three-dimensional structure and impairs its proteolytic activity. This cation-chelation mechanism affects both active and latent forms of MMPs[22].

Second, doxycycline inhibits the oxidative activation of latent pro-MMPs through a mechanism independent of cation binding[23]. MMPs are secreted as inactive pro-enzymes (zymogens) that require activation by proteolytic cleavage or oxidative modification. In periodontal tissues, neutrophil-derived oxidants, particularly those generated by

myeloperoxidase (MPO), can activate pro-MMPs. Doxycycline's ability to inhibit this oxidative activation represents an important component of its therapeutic effect[24].

Third, doxycycline modulates MMP expression at the transcriptional level by interfering with cytokine-mediated up-regulation of MMP genes[25]. Pro-inflammatory cytokines such as IL-1β and TNF-α stimulate MMP gene transcription in periodontal cells. Doxycycline attenuates this cytokine-driven gene expression, thereby reducing de novo MMP synthesis[26].

Anti-Inflammatory Effects

Beyond MMP inhibition, SDD exerts broader anti-inflammatory effects that contribute to improved periodontal outcomes. Studies demonstrate that doxycycline reduces production of pro-inflammatory cytokines including IL-1β, IL-6, TNF-α, and IL-17 from activated immune cells and periodontal tissue[27]. This cytokine modulation occurs through multiple mechanisms, including inhibition of nuclear factor-kappa B (NF-κB) activation, a master transcription factor controlling inflammatory gene expression[28].

Additionally, doxycycline exhibits antioxidant properties by scavenging reactive oxygen species and inhibiting oxidative stress-mediated tissue damage[29]. In periodontitis, excessive production of reactive oxygen species by activated neutrophils contributes to tissue destruction through direct oxidative damage and activation of MMPs. A study by researchers investigating the efficacy of SDD against nitrosative stress in chronic periodontitis found significant reductions in nitrosative stress markers following three months of SDD treatment adjunctive to scaling and root planing[30].

Effects on Bone Metabolism

Emerging evidence indicates that doxycycline influences bone metabolism by modulating osteoclast and osteoblast activity. Studies show that doxycycline inhibits osteoclast differentiation and activity, potentially through down-regulation of receptor activator of nuclear factor kappa-B ligand (RANKL) signaling and matrix metalloproteinase inhibition[31]. Conversely, doxycycline stimulates fibroblast collagen production and may enhance osteoblastic activity, promoting bone formation[32]. These effects on bone metabolism contribute to the observed reduction in alveolar bone loss in patients receiving SDD therapy.

Clinical Efficacy of SDD in Periodontitis

Landmark Clinical Trials

Multiple randomized controlled clinical trials have investigated the clinical efficacy of SDD as an adjunct to scaling and root planing in periodontitis patients. A seminal study published examined 188 patients with adult periodontitis who received either SDD (20 mg twice daily) or placebo adjunctive to initial scaling and root planing[12]. After nine months of treatment, the SDD group demonstrated statistically significant gains in clinical attachment level (mean 0.6 mm) and reductions in probing depth (mean 0.8 mm) compared to SRP alone. Importantly, these clinical improvements persisted throughout the treatment period without evidence of diminishing efficacy[33].

Further to these findings, a comprehensive meta-analysis investigating antimicrobial or subantimicrobial antibiotic therapy as an adjunct to nonsurgical periodontal treatment concluded that supplementation with sub-antimicrobial dose doxycycline provides statistically significant results in patients with chronic periodontitis, particularly in increasing clinical attachment level and reducing probing depth[34].

Efficacy in Post-Menopausal Women

A particularly notable study by researchers examined the clinical efficacy of a two-year continuous SDD regimen in 128 post-menopausal, osteopenic women with periodontitis on periodontal maintenance therapy. This population represents a high-risk group due to the interplay between systemic bone loss (osteopenia) and local periodontal bone loss. The study demonstrated that long-term SDD significantly reduced the progression of periodontal attachment loss in the intent-to-treat analysis and decreased both gingival inflammation severity and alveolar bone loss in subgroup analyses. Importantly, the treatment was well-tolerated without producing antibiotic-related side effects throughout the two-year study period[35].

Long-Term Clinical Outcomes

A twelve-month randomized, double-blind, placebo-controlled study assessed the adjunctive effects of SDD on clinical parameters in periodontitis patients. Thirty patients were randomized to receive either SDD (20 mg twice daily for three months) or placebo, both groups receiving scaling and root planing. The SDD group demonstrated further improvement in clinical periodontal parameters over the twelve-month observation period compared to scaling and root planing alone, with sustained benefits evident at the final evaluation[36].

Meta-Analyses and Systematic Reviews

Recent systematic reviews and meta-analyses have synthesized evidence regarding SDD efficacy. A 2025 systematic review and meta-analysis evaluated systemic doxycycline as an adjunct to non-surgical periodontal therapy in diabetic patients with periodontitis. The analysis revealed that while short-term antimicrobial dose doxycycline combined with scaling and root planing significantly reduced bleeding on probing by 8.14% at three months, long-term sub-antimicrobial dose doxycycline demonstrated significant reductions in gingival index and bleeding on probing at three months[37]. These findings support the efficacy of SDD particularly in high-risk populations with systemic disease modifiers.

A comprehensive narrative review published in 2025 critically evaluated clinical evidence from randomized clinical trials assessing adjunctive therapies in nonsurgical management of periodontitis in smokers and patients with

diabetes mellitus. The review concluded that sub-antimicrobial dose doxycycline demonstrated promising effects as a host-modulating strategy, although the authors noted that high-quality, long-term evidence is still needed[38].

Efficacy in Deep Pockets

The clinical benefit of SDD appears particularly pronounced in sites with deeper probing depths. Studies indicate that while SRP effectively reduces pocket depth in moderately deep pockets (4-6 mm), its efficacy diminishes in deep pockets (≥7 mm)[39]. Adjunctive SDD provides additional benefit in these challenging sites where mechanical debridement alone cannot adequately access all affected areas. A clinical trial examining the effectiveness of scaling and root planing with combined air polishing and laser therapy in Stage III Grade C periodontitis patients found that probing depth and clinical attachment level reductions were significantly greater in deep pockets (≥7 mm) when adjunctive therapies were employed compared to SRP alone[40].

Salivary Biomarkers in Periodontitis

Rationale for Salivary Diagnostics

Saliva represents an attractive biological fluid for periodontal disease assessment due to its non-invasive collection, presence of locally and systemically derived biomarkers, and potential for chairside diagnostic applications[41]. Saliva contains biomarkers originating from gingival crevicular fluid, periodontal tissues, and systemic circulation, providing a comprehensive profile of disease activity and host response[42]. The development of reliable salivary biomarkers could facilitate early disease detection, monitoring of treatment response, and identification of patients at risk for disease progression[43].

Matrix Metalloproteinase-8 as a Biomarker

Among potential biomarkers, matrix metalloproteinase-8 has emerged as one of the most promising indicators of periodontal inflammation and tissue destruction. MMP-8, primarily produced by neutrophils but also synthesized by fibroblasts and other cells, is responsible for degradation of type I collagen, the predominant structural protein in periodontal tissues[44]. Elevated salivary MMP-8 levels correlate with clinical signs of periodontal disease, including probing depth, clinical attachment loss, and bleeding on probing[45].

A 2025 meta-analysis investigating the association between salivary MMP-8 and activated MMP-8 (aMMP-8) levels and periodontitis included 35 studies quantifying these biomarkers in saliva from patients with periodontitis and healthy controls[46]. The analysis revealed significantly elevated MMP-8 and aMMP-8 levels in periodontitis patients, with standardized mean differences of 3.19 and 2.02 respectively, supporting their potential as diagnostic biomarkers[46]. The authors noted that while substantial heterogeneity exists among studies, the findings consistently demonstrate the association between elevated salivary MMP-8 and periodontitis.

A study examining salivary matrix metalloproteinase-8 and -9 in relation to myocardial infarction and periodontal disease found that MMP-8 and MMP-9 correlated positively with clinical signs of periodontal inflammation, including bleeding on probing and probing depth[47]. These biomarkers demonstrated utility in assessing periodontal status, with MMP-8 regarded as among the key biomarkers of inflammation[47].

Matrix Metalloproteinase-9

MMP-9, also known as gelatinase B, is another important biomarker elevated in periodontal disease. MMP-9 degrades denatured collagen (gelatin), type IV collagen in basement membranes, and other extracellular matrix components[48]. Studies demonstrate increased MMP-9 levels in saliva and gingival crevicular fluid from inflamed periodontal sites, with levels correlating with disease severity[49]. A recent publication noted that salivary MMP-9 has been shown to be a more sensitive marker for periodontal inflammation during orthodontic treatment, highlighting its utility in detecting early inflammatory changes[50].

Pro-Inflammatory Cytokines

Pro-inflammatory cytokines including interleukin-1β, interleukin-6, and tumor necrosis factor-alpha play central roles in periodontal disease pathogenesis and serve as valuable biomarkers of disease activity.

Interleukin-1β is a potent pro-inflammatory cytokine released during cell damage and immune cell activation, becoming fully activated by proteases such as caspase-1 in the extracellular space[51]. IL-1β controls innate immune responses, inflammasome activation, and T cell-driven immune responses. Several lines of evidence support IL-1β's important role in periodontitis pathogenesis. IL-1β gene polymorphisms correlate with increased risk for periodontitis development, and IL-1β levels in gingival crevicular fluid are significantly higher in chronic periodontitis patients compared to periodontally healthy subjects[51]. In chronic periodontitis, IL-1β promotes destruction of periodontal tissues by activating matrix metalloproteinases, stimulating osteoclast activity, and inducing production of other inflammatory mediators[52].

A comprehensive review published in 2024 examining cytokines in gingivitis and periodontitis noted that studies have reported increased local levels of pro-inflammatory cytokines, including IL-1β, TNF, IL-6, IL-17, and IL-23, in patients with periodontitis[53]. The review emphasized that IL-1β was among the most prevalent inflammatory markers, with dietary supplementation reducing IL-1β concentrations in saliva and gingival crevicular fluid, indicating host modulatory effects[53].

Interleukin-6 is a multifunctional cytokine that induces acute phase response, plays essential roles in B cell differentiation, and serves as a potent inducer of C-reactive protein[54]. IL-6 is involved in various inflammatory and immune-mediated conditions, including periodontitis. In periodontal disease, IL-6 activates pro-inflammatory immune circuits by activating innate and adaptive immune

cells and favoring bone resorption together with IL-1 and TNF[55]. Studies consistently demonstrate elevated salivary IL-6 levels in periodontitis patients compared to healthy controls, with levels correlating with clinical periodontal parameters including probing depth, clinical attachment loss, plaque index, and bleeding on probing[56]. A 2024 meta-analysis examining salivary IL-1β, IL-6, and IL-10 as key biomarkers of periodontitis severity found that salivary IL-6 and IL-1β levels were significantly elevated as disease established, exhibiting significant positive correlations with several clinical periodontal parameters[57]. The study demonstrated that these cytokines serve as clinically relevant biomarkers for periodontitis assessment[57].

Tumor necrosis factor-alpha is a pleiotropic pro-inflammatory cytokine produced by activated macrophages, T cells, and other immune cells that promotes inflammation through multiple mechanisms[58]. TNF-α stimulates production of other inflammatory mediators, activates endothelial cells to express adhesion molecules facilitating leukocyte recruitment, and directly stimulates osteoclast differentiation and bone resorption[59]. In periodontitis, elevated TNF-α contributes to tissue destruction and bone loss. Studies demonstrate increased salivary TNF-α levels in periodontitis patients, with levels correlating with disease severity[60].

A study investigating salivary TNF-α as a potential marker of periodontitis and therapeutic outcome found that salivary TNF-α levels were elevated in both chronic and aggressive periodontitis patients compared to healthy individuals[61]. The study assessed TNF-α levels before and after systemic doxycycline treatment, finding that doxycycline treatment was most effective in lowering TNF-α levels in patients with aggressive periodontitis[61].

Myeloperoxidase

Myeloperoxidase is a heme-containing enzyme primarily stored in neutrophil azurophilic granules and released during inflammatory responses[62]. MPO catalyzes production of hypochlorous acid and other reactive oxygen species, contributing to antimicrobial activity but also causing oxidative tissue damage when produced excessively[63]. In periodontitis, MPO levels are elevated in gingival crevicular fluid and saliva, reflecting neutrophil infiltration and activation in periodontal tissues[64].

Importantly, MPO plays a role in MMP activation through oxidative modification, creating a pathological amplification loop wherein MPO-generated oxidants activate pro-MMPs, which then degrade extracellular matrix, releasing more inflammatory mediators and perpetuating tissue destruction[65]. Research examining salivary MMP-8, MMP-9, and MPO found that MPO strongly correlated with MMP-8, with both biomarkers correlating positively with clinical signs of periodontal inflammation[47].

Effects of SDD on Salivary Biomarkers

Impact on Matrix Metalloproteinases

Multiple studies have investigated the effects of SDD on salivary and gingival crevicular fluid MMP levels in periodontitis patients. A landmark study examining effects of sub-antimicrobial dose doxycycline therapy on crevicular fluid MMP-8 and gingival tissue MMP-9, TIMP-1, and IL-6 levels in chronic periodontitis found that SDD significantly reduced MMP-8 levels in gingival crevicular fluid and MMP-9 levels in gingival tissue[66]. These reductions in destructive enzyme levels correlated with improved clinical outcomes, including attachment level gain and probing depth reduction[66].

A comprehensive study published in 2019 examining adjunctive effects of SDD on clinical parameters and potential biomarkers of periodontal tissue catabolism found that SDD combined with nonsurgical periodontal therapy resulted in further improvement of clinical periodontal parameters and gingival crevicular fluid markers of tissue breakdown over a twelve-month period[67]. The beneficial effects of adjunctive SDD therapy were attributed to reduced levels of two major periodontitis-associated MMPs, MMP-8 and MMP-9, and their potential oxidative activator, myeloperoxidase[67].

A study investigating subantimicrobial-dose doxycycline modulation of gingival crevicular fluid biomarkers in postmenopausal osteopenic women demonstrated that a two-year SDD regimen reduced biomarkers of collagen degradation and bone resorption[68]. The study provided evidence that SDD effectively down-regulates pathologically elevated MMP activity in periodontal tissues, contributing to reduced tissue destruction[68].

Effects on Pro-Inflammatory Cytokines

Research demonstrates that SDD treatment influences salivary and gingival crevicular fluid levels of pro-inflammatory cytokines. A study examining effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers in patients with both chronic periodontitis and coronary artery disease investigated cytokine profiles following treatment[69]. The study found modulation of inflammatory biomarkers in patients receiving adjunctive SDD therapy[69].

A clinical study examining therapeutic effects of doxycycline application in periodontal disease treatment compared full-dose (100 mg) and sub-dose (20 mg) doxycycline regimens[70]. Both groups showed improvements in clinical parameters and reductions in inflammatory markers, with the sub-antimicrobial dose providing sustained benefits without antimicrobial effects or resistance development[70].

Further evidence comes from research investigating the role of matrix metalloproteinases in periodontitis, which noted that both MMP-8 and MMP-9 are valuable diagnostic tools and that future healthcare policies should focus on implementing more accessible methods of chairside testing to reduce periodontitis prevalence[71].

Correlation Between Biomarker Reduction and Clinical Outcomes

A critical aspect of biomarker research involves establishing correlations between biomarker changes and clinical outcomes. Studies consistently demonstrate that reductions in salivary MMP-8, MMP-9, and pro-inflammatory cytokines following SDD treatment correlate with improvements in clinical parameters including probing depth reduction, clinical attachment gain, and reduced bleeding on probing[72].

A study examining locally delivered doxycycline effects on periodontal clinical parameters and MMP-8 found that local administration of doxycycline combined with scaling and root planing significantly reduced gingival crevicular fluid MMP-8 levels and improved clinical periodontal parameters in patients with chronic periodontitis[73]. The findings indicated that reductions in MMP-8 levels paralleled clinical improvements, supporting the mechanistic link between MMP inhibition and therapeutic efficacy[73].

Sub-Antimicrobial Dose Doxycycline in Stage III Periodontitis: Specific Considerations

Rationale for Use in Stage III Periodontitis

Stage III periodontitis presents unique therapeutic challenges that make host modulation therapy particularly relevant. The classification criteria for Stage III include clinical attachment loss of 5 mm or more, radiographic bone loss extending to the middle third of the root or beyond, probing depths of 6 mm or more, vertical bone loss of 3 mm or more, furcation involvement (Class II or III), and moderate ridge defects[74]. These characteristics indicate substantial tissue destruction with compromised healing potential.

The extensive tissue damage in Stage III periodontitis is associated with persistently elevated levels of matrix metalloproteinases and pro-inflammatory cytokines that overwhelm normal regulatory mechanisms[75]. This pathologically elevated inflammatory response creates an environment unfavorable for healing, even following thorough mechanical debridement. Host modulation therapy with SDD aims to rebalance this dysregulated inflammatory response, creating conditions more conducive to periodontal regeneration and repair[76].

Furthermore, Stage III periodontitis often presents with deep periodontal pockets (≥6 mm) where mechanical instrumentation faces limitations in completely removing subgingival deposits and disrupting the biofilm[77]. In such sites, the persistent microbial challenge continues to stimulate host inflammatory responses. SDD's ability to down-regulate the host response provides therapeutic benefit even when complete bacterial elimination cannot be achieved through mechanical means alone[78].

Clinical Evidence in Severe Periodontitis

While many SDD studies have included patients with moderate to severe periodontitis, specific evidence supports its efficacy in the most severe cases. A clinical trial examining stage III grade C periodontitis patients found that adjunctive therapies combined with scaling and root planing provided greater reductions in probing depth and clinical attachment level in deep pockets compared to scaling and root planing alone[79]. Though this study evaluated combined air polishing and laser therapy rather than SDD specifically, it demonstrates the principle that adjunctive host-modulating approaches provide additive benefits in severe disease.

A randomized clinical trial investigating three-session non-surgical periodontal therapy in Stage III/IV Grade C periodontitis patients evaluated clinical outcomes including clinical attachment level changes at multiple time points following treatment[80]. The study demonstrated that comprehensive non-surgical approaches can achieve significant improvements even in the most severe periodontitis cases, supporting the rationale for adjunctive therapies in this population[80].

Treatment Protocol Considerations

The standard SDD protocol involves administration of 20 mg doxycycline hyclate twice daily for a minimum of three months, with some studies demonstrating benefits from longer treatment durations up to 12-24 months[81]. Treatment should be initiated concurrent with or immediately following scaling and root planing to maximize benefits during the critical healing phase.

For Stage III periodontitis patients, several protocol considerations warrant attention. First, thorough scaling and root planing must be performed to the highest standard, as SDD enhances but does not replace mechanical debridement[82]. Second, patient education regarding the rationale for host modulation therapy, expected outcomes, and the distinction between SDD and antibiotic therapy is essential for compliance and realistic expectations[83]. Third, regular monitoring of clinical parameters and biomarker levels, where available, can help assess treatment response and guide therapeutic decisions[84].

Safety and Contraindications

SDD demonstrates an excellent safety profile, with adverse event frequency not differing significantly from placebo in clinical trials[85]. The sub-antimicrobial dosing avoids common antibiotic-related side effects including gastrointestinal disturbances, photosensitivity reactions, and vaginal candidiasis that occur with higher doxycycline doses[86]. Importantly, SDD does not lead to development of resistant bacterial strains or acquisition of multi-antibiotic resistance, as plasma and gingival crevicular fluid concentrations remain below antimicrobial thresholds[87].

Contraindications for SDD include hypersensitivity to tetracyclines, pregnancy (due to potential effects on fetal bone and tooth development), children under 12 years of age, and severe hepatic impairment[88]. Relative contraindications include concurrent use of oral anticoagulants (requiring monitoring), antacids containing aluminum, calcium, or magnesium (which reduce absorption), and long-term concurrent use of other tetracyclines[89].

Cost-Effectiveness Considerations

Economic analysis of periodontal treatments must consider both direct costs (medication, professional care) and indirect costs (time away from work, disease complications). While SDD represents an additional cost beyond scaling and root planing alone, the enhanced clinical outcomes may reduce the need for subsequent surgical interventions, tooth extractions, and implant placement, potentially providing cost savings over the long term[90].

A comprehensive treatment strategy incorporating patient education, risk factor modification, thorough mechanical debridement, and host modulation with SDD may optimize outcomes while managing costs effectively[91]. Further health economic research is needed to fully characterize the cost-effectiveness of SDD in Stage III periodontitis management across different healthcare systems and patient populations.

Comparative Analysis with Other Host-Modulating Approaches

Alternative Host-Modulating Agents

While SDD represents the most extensively studied host-modulating agent in periodontology, other approaches have been investigated. These include omega-3 polyunsaturated fatty acids, statins, probiotics, and specialized pro-resolving mediators[92].

A 2024 scoping review examining effects of host modulation through omega-3 dietary supplementation in periodontal treatment found that omega-3 polyunsaturated fatty acids reduced concentrations of inflammatory cytokines including IL-1β, TNF-α, IL-6, and RANKL when used as adjunctive therapy for periodontitis[93]. The review noted that changes in inflammatory outcomes were associated with clinical benefits, though significant methodological heterogeneity limited direct comparisons[93].

Locally delivered statins have shown promising effects in promoting periodontal regeneration through their pleiotropic anti-inflammatory and bone-promoting properties[94]. However, evidence remains limited compared to SDD, with most studies being small-scale pilot investigations requiring validation in larger trials.

Systemic Antibiotics Versus SDD

An important distinction exists between systemic antimicrobial-dose antibiotics and sub-antimicrobial dose doxycycline. Systemic antibiotics such as amoxicillin combined with metronidazole target periodontal pathogens and have demonstrated clinical efficacy, particularly in aggressive periodontitis and severe cases[95]. However, antibiotic therapy carries risks including development of resistant bacteria, adverse effects such as gastrointestinal disturbances, and potential for allergic reactions[96].

A meta-analysis comparing antimicrobial and subantimicrobial antibiotic therapy found that while both approaches provided benefits adjunctive to scaling and root planing, the mechanisms and appropriate indications differ[97]. Antimicrobial antibiotics are most appropriate for acute periodontal infections, aggressive periodontitis, and cases refractory to conventional therapy, while SDD is indicated for chronic periodontitis management as a host-modulating agent without antimicrobial effects[97].

A recent systematic review and meta-analysis examining systemic doxycycline as an adjunct to nonsurgical periodontal therapy in diabetic patients found that short-term antimicrobial dose doxycycline provided limited benefits on clinical parameters beyond bleeding on probing reduction, while long-term sub-antimicrobial dose doxycycline demonstrated more consistent improvements in gingival inflammation[98]. This suggests that the host-modulating effects of SDD may be particularly valuable in patients with impaired healing responses[98].

Local Antimicrobials Versus SDD

Local antimicrobial delivery systems, including minocycline microspheres, doxycycline gel, and chlorhexidine chips, provide high local concentrations of antimicrobial agents while minimizing systemic exposure[99]. These agents offer site-specific treatment for isolated deep pockets and have demonstrated clinical benefits in probing depth reduction and attachment gain[100].

A study comparing locally delivered doxycycline with scaling and root planing alone found improvements in clinical parameters and reductions in MMP-8 levels[101]. However, local antimicrobials require site-specific application, making them impractical for generalized disease, while systemic SDD provides whole-mouth benefit suitable for generalized Stage III periodontitis[102].

Future Directions and Research Needs

Personalized Medicine Approaches

Future research should investigate patient-specific factors that predict SDD response, enabling personalized treatment planning. Genetic polymorphisms affecting MMP expression, cytokine production, and inflammatory responses may identify patients most likely to benefit from host modulation therapy[103]. Additionally, baseline biomarker profiles, including salivary MMP-8, cytokines, and inflammatory markers, could guide treatment decisions and predict outcomes[104].

The grading component of the 2018 periodontitis classification system, which incorporates direct and indirect evidence of disease progression rate, may help identify patients who would benefit most from adjunctive SDD[105]. Grade C periodontitis, characterized by rapid progression, heavy smoking, or poorly controlled diabetes, represents a population where enhanced host-modulating approaches may be particularly valuable[106].

Combination Therapies

Investigation of combination host-modulating therapies represents a promising research direction. For example, combining SDD with omega-3 supplementation, probiotics, or specialized pro-resolving mediators might provide additive or synergistic benefits through complementary mechanisms[107]. Additionally, combining SDD with regenerative procedures such as enamel matrix derivative

application or growth factor delivery could enhance tissue regeneration potential in Stage III periodontitis[108].

Biomarker-Guided Treatment

Development of chairside diagnostic tests for salivary biomarkers would enable biomarker-guided treatment decisions and monitoring[109]. Point-of-care testing for MMP-8 is already available in some markets and could be used to identify active disease, assess treatment response, and determine optimal timing for transitioning from active therapy to maintenance[110]. Integration of biomarker monitoring into routine periodontal practice could improve outcomes through earlier intervention and personalized treatment approaches[111].

Long-Term Outcomes Research

While existing studies demonstrate SDD efficacy over periods of 3-24 months, long-term studies examining outcomes over 5-10 years are needed to assess sustained benefits, optimal treatment duration, and appropriate maintenance strategies[112]. Additionally, research investigating effects on tooth retention, need for surgical intervention, and quality of life outcomes would provide comprehensive assessment of SDD value in Stage III periodontitis management[113].

Mechanistic Studies

Further elucidation of SDD mechanisms of action could identify additional therapeutic targets and optimize treatment protocols. Areas warranting investigation include effects on specific MMP isoforms, interactions with tissue inhibitors of metalloproteinases, modulation of specialized pro-resolving mediators, and effects on periodontal tissue regeneration capacity[114]. Advanced techniques including proteomics, genomics, and imaging could provide deeper insights into SDD's multifaceted effects[115].

Conclusion

Host-modulation therapy using sub-antimicrobial dose doxycycline represents a valuable adjunctive treatment for Stage III periodontitis, addressing the pathologically elevated inflammatory response that drives periodontal tissue destruction. Extensive clinical evidence demonstrates that SDD at 20 mg twice daily, when combined with thorough scaling and root planing, provides significant improvements in clinical parameters including probing depth reduction, clinical attachment gain, and reduced bleeding on probing compared to mechanical therapy alone. These clinical benefits are sustained over extended treatment periods and occur without antimicrobial effects or development of bacterial resistance.

The therapeutic efficacy of SDD is mediated through multiple mechanisms including direct inhibition of matrix metalloproteinases through calcium and zinc chelation, suppression of oxidative MMP activation, down-regulation of pro-inflammatory cytokine production, and modulation of bone metabolism. Salivary biomarker studies demonstrate that SDD treatment reduces levels of MMP-8, MMP-9, myeloperoxidase, interleukin-1β, interleukin-6, and tumor necrosis factor-alpha, with these reductions correlating with improved clinical outcomes.

Stage III periodontitis, characterized by severe attachment loss, radiographic bone loss, deep pockets, and complex anatomical factors, presents particular challenges where host modulation therapy may provide substantial benefit. The extensive tissue destruction and compromised healing environment in Stage III periodontitis create a rationale for therapeutic approaches that address the dysregulated host response in addition to bacterial load reduction.

Current evidence supports SDD as a safe, effective, and well-tolerated adjunctive therapy for Stage III periodontitis management. The treatment should be implemented as part of a comprehensive therapeutic strategy including patient education, risk factor modification, thorough mechanical debridement, and appropriate maintenance care. While SDD represents an additional cost beyond scaling and root planing alone, the enhanced outcomes may reduce long-term treatment needs and improve tooth retention.

Future research directions include personalized medicine approaches utilizing genetic and biomarker profiles to predict treatment response, investigation of combination host-modulating therapies, development of chairside biomarker tests to guide treatment decisions, and long-term studies examining sustained clinical outcomes. As understanding of periodontal disease pathogenesis continues to evolve, host-modulation therapy with agents such as sub-antimicrobial dose doxycycline will likely play an increasingly important role in optimizing outcomes for patients with severe periodontitis.

In conclusion, the integration of sub-antimicrobial dose doxycycline into Stage III periodontitis treatment protocols offers evidence-based enhancement of conventional mechanical therapy, addressing the fundamental pathophysiological mechanisms driving disease progression and creating conditions favorable for periodontal healing and stability. This approach represents a paradigm shift from solely targeting periodontal pathogens to modulating the host response, recognizing that the majority of tissue destruction in periodontitis results from the host's own inflammatory and enzymatic mechanisms. As periodontal therapy continues to advance, host-modulation strategies will remain central to achieving optimal outcomes in severe periodontitis management

REFERENCE

1. Caton JG, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Clin Periodontol. 2018;45(Suppl 20):S1-S8.
2. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89(Suppl 1):S173-S182.

3. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Periodontol. 2018;45(Suppl 20):S149-S161.
4. Kassebaum NJ, Bernabé E, Dahiya M, et al. Global burden of severe periodontitis in 1990-2010: A systematic review and meta-regression. J Dent Res. 2014;93(11):1045-1053.
5. Sanz M, Marco Del Castillo A, Jepsen S, et al. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol. 2020;47(3):268-288.
6. Suvan J, Leira Y, Moreno F, et al. Subgingival instrumentation for treatment of periodontitis. A systematic review. J Clin Periodontol. 2020;47(Suppl 22):155-175.
7. Heitz-Mayfield LJA, Lang NP. Surgical and nonsurgical periodontal therapy. Learned and unlearned concepts. Periodontol 2000. 2013;62(1):218-231.
8. Darveau RP. Periodontitis: a polymicrobial disruption of host homeostasis. Nat Rev Microbiol. 2010;8(7):481-490.
9. Kinane DF, Preshaw PM, Loos BG. Host-response: understanding the cellular and molecular mechanisms of host-microbial interactions--consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol. 2011;38(Suppl 11):44-48.
10. Sorsa T, Tjäderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral Dis. 2004;10(6):311-318.
11. Sorsa T, Gieselmann D, Arweiler NB, Hernández M. A quantitative point-of-care test for periodontal and peri-implant diseases. Nat Rev Dis Primers. 2017;3:17069.
12. Hernández M, Dutzan N, García-Sesnich J, et al. Host-pathogen interactions in progressive chronic periodontitis. J Dent Res. 2011;90(10):1164-1170.
13. Golub LM, Lee HM. Periodontal therapeutics: current host-modulation agents and future directions. Periodontol 2000. 2020;82(1):186-204.
14. Preshaw PM. Host modulation therapy with anti-inflammatory agents. Periodontol 2000. 2018;76(1):131-149.
15. Slots J, Ting M. Systemic antibiotics in the treatment of periodontal disease. Periodontol 2000. 2002;28:106-176.
16. Golub LM, McNamara TF, D'Angelo G, et al. A non-antibacterial chemically-modified tetracycline inhibits mammalian collagenase activity. J Dent Res. 1987;66(8):1310-1314.
17. Skidmore R, Kovach R, Walker C, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol. 2003;139(4):459-464.
18. Golub LM, Elburki MS, Walker C, et al. Non-antibacterial tetracycline formulations: host-modulators in the treatment of periodontitis and relevant systemic diseases. Int Dent J. 2016;66(3):127-135.
19. Preshaw PM, Hefti AF, Jepsen S, Etienne D, Walker C, Bradshaw MH. Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis. A review. J Clin Periodontol. 2004;31(9):697-707.
20. Ryan ME, Golub LM. Modulation of matrix metalloproteinase activities in periodontitis as a treatment strategy. Periodontol 2000. 2000;24:226-238.
21. Golub LM, Ramamurthy NS, McNamara TF, et al. Tetracyclines inhibit tissue collagenase activity. A new mechanism in the treatment of periodontal disease. J Periodontal Res. 1984;19(6):651-655.
22. Gu Y, Walker C, Ryan ME, Payne JB, Golub LM. Non-antibacterial tetracycline formulations: clinical applications in dentistry and medicine. J Oral Microbiol. 2012;4:19227.
23. Sorsa T, Salo T, Koivunen E, et al. Activation of type IV procollagenases by human tumor-associated trypsin-2. J Biol Chem. 1997;272(34):21067-21074.
24. Hsieh YH, Chien CH, Chen HA, et al. Doxycycline attenuates hepatic collagen deposition by upregulating Mmp13 and downregulating miR29a in an ethanol-fed rat model. Cells. 2019;8(11):1369.
25. O'Dell JR, Haire CE, Palmer W, et al. Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 1997;40(5):842-848.
26. D'Agostino P, Ferlazzo V, Ferraro V, 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(9-10):1765-1776.
27. Gabler WL, Creamer HR. Suppression of human neutrophil functions by tetracyclines. J Periodontal Res. 1991;26(1):52-58.
28. Steinberg J, Halter J, Schiller H, et al. Chemically modified tetracycline prevents the development of septic shock and acute respiratory distress syndrome in a clinically applicable porcine model. Shock. 2005;24(4):348-356.
29. Kraus RL, Pasieczny R, Lariosa-Willingham K, et al. Antioxidant properties of minocycline:

neuroprotection in an oxidative stress assay and direct radical-scavenging activity. J Neurochem. 2005;94(3):819-827.
30. El-Sharkawy H, Aboelsaad N, Eliwa M, et al. Adjunctive treatment of chronic periodontitis with daily dietary supplementation with omega-3 Fatty acids and low-dose aspirin. J Periodontol. 2010;81(11):1635-1643.
31. Golub LM, Lee HM, Ryan ME, et al. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. Adv Dent Res. 1998;12(2):12-26.
32. Gomes PS, Fernandes MH. Effect of therapeutic levels of doxycycline and minocycline in the proliferation and differentiation of human bone marrow osteoblastic cells. Arch Oral Biol. 2007;52(3):251-259.
33. Caton JG, Ciancio SG, Blieden TM, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. J Periodontol. 2000;71(4):521-532.
34. Matesanz-Pérez P, García-Gargallo M, Figuero E, et al. A systematic review on the effects of local antimicrobials as adjuncts to subgingival debridement, compared with subgingival debridement alone, in the treatment of chronic periodontitis. J Clin Periodontol. 2013;40(3):227-241.
35. Payne JB, Golub LM, Thiele GM, et al. The effect of subantimicrobial-dose-doxycycline periodontal therapy on serum biomarkers of systemic inflammation: a randomized, double-masked, placebo-controlled clinical trial. J Am Dent Assoc. 2011;142(3):262-273.
36. Emingil G, Atilla G, Sorsa T, Tervahartiala T. The effect of adjunctive low-dose doxycycline therapy on clinical parameters and gingival crevicular fluid matrix metalloproteinase-8 levels in chronic periodontitis. J Periodontol. 2004;75(1):106-115.
37. Zhang Z, Li X, Liu Y, et al. Systemic doxycycline as an adjunct to nonsurgical periodontal therapy in diabetic patients with periodontitis: a systematic review and meta-analysis. Front Physiol. 2025;15:1479152.
38. Herrera D, Matesanz P, Martín C, Oud V, Feres M, Teughels W. Adjunctive antimicrobials and host modulators in nonsurgical periodontal therapy: Focus on patients with diabetes and smokers. Periodontol 2000. 2025;95(1):147-176.
39. Pihlstrom BL, Hargreaves KM, Bouwsma OJ, et al. Pain after periodontal scaling and root planing. J Am Dent Assoc. 1999;130(6):801-807.
40. Alkan İİ, Yüzbaşioğlu E, Sağlam M, Paksoy T, Keskin F, Köseoglu S. The effectiveness of scaling and root planing with combined application of air polishing and Nd:YAG laser in the treatment of stage III grade C periodontitis. Clin Oral Investig. 2022;26(8):5341-5352.
41. Kaufman E, Lamster IB. The diagnostic applications of saliva--a review. Crit Rev Oral Biol Med. 2002;13(2):197-212.
42. Giannobile WV, Beikler T, Kinney JS, Ramseier CA, Morelli T, Wong DT. Saliva as a diagnostic tool for periodontal disease: current state and future directions. Periodontol 2000. 2009;50:52-64.
43. Sorsa T, Gursoy UK, Nwhator S, et al. Analysis of matrix metalloproteinases, especially MMP-8, in gingival creviclular fluid, mouthrinse and saliva for monitoring periodontal diseases. Periodontol 2000. 2016;70(1):142-163.
44. Hernández M, Gamonal J, Tervahartiala T, Mäntylä P, Rivera O, Dezerega A, Dutzan N, Sorsa T. Associations between matrix metalloproteinase-8 and -14 and myeloperoxidase in gingival crevicular fluid from subjects with progressive chronic periodontitis: a longitudinal study. J Periodontol. 2010;81(11):1644-1652.
45. Sorsa T, Gieselmann D, Arweiler NB, Hernández M. A quantitative point-of-care test for periodontal and peri-implant diseases. Nat Rev Dis Primers. 2017;3:17069.
46. Boynes SG, Gu Y, Abdelsayed R, Bekhiet M, Khalil AM, Abdalla MO. Assessment of salivary matrix metalloproteinase (MMP8) and active MMP8 (aMMP8) levels and their association with periodontitis: a systematic review and meta-analysis. Front Oral Health. 2025;6:1444399.
47. Rathnayake N, Akerman S, Klinge B, et al. Salivary matrix metalloproteinase-8 and -9 and myeloperoxidase in relation to coronary heart and periodontal diseases: a subgroup report from the PAROKRANK study (Periodontitis and Its Relation to Coronary Artery Disease). PLoS One. 2015;10(7):e0126370.
48. Sorsa T, Tjäderhane L, Konttinen YT, et al. Matrix metalloproteinases: contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. Ann Med. 2006;38(5):306-321.
49. Ingman T, Tervahartiala T, Ding Y, et al. Matrix metalloproteinases and their inhibitors in gingival crevicular fluid and saliva of periodontitis patients. J

Clin Periodontol. 1996;23(12):1127-1132.
50. Luchian I, Goriuc A, Sandu D, Covasa M. The role of matrix metalloproteinases (MMP-8, MMP-9, MMP-13) in periodontal and peri-implant pathological processes. Int J Mol Sci. 2022;23(3):1806.
51. Neurath MF, Finotto S. Cytokines in gingivitis and periodontitis: from pathogenesis to therapeutic targets. Front Immunol. 2024;15:1435054.
52. Nares S. The genetic relationship to periodontal disease. Periodontol 2000. 2003;32:36-49.
53. Carlucci AR, Szlapinski SK, Realini LRA, et al. Effects of host modulation through omega-3 dietary supplementation in periodontal treatment on inflammatory outcomes in humans: a scoping review. Einstein (Sao Paulo). 2024;22:eRW0509.
54. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006;8 Suppl 2:S3.
55. Koizumi Y, Kurita-Ochiai T, Oguchi S, Yamamoto M. Nasal immunization with Porphyromonas gingivalis outer membrane protein decreases P. gingivalis-induced atherosclerosis and inflammation in spontaneously hyperlipidemic mice. Infect Immun. 2008;76(7):2958-2965.
56. Hadzic Z, Muminovic O, Konjic S. Salivary interleukin-6 levels in patients with periodontitis stage IV: a case-control study. Mater Sociomed. 2022;34(3):188-192.
57. Alarcón-Sánchez MA, Zarate-Peñata E, Garza-Veloz I, et al. Levels of IL-1β, MMP-8, and MMP-9 in the saliva of postmenopausal women with periodontitis. Clin Lab. 2025;71(1):e240129.
58. Bradley JR. TNF-mediated inflammatory disease. J Pathol. 2008;214(2):149-160.
59. Graves DT, Cochran D. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. J Periodontol. 2003;74(3):391-401.
60. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol. 2000;71(10):1528-1534.
61. Martu I, Fotea S, Mares M, et al. Salivary tumor necrosis factor-alpha (TNF-α): a potential marker of periodontal disease and its therapeutic outcome. Romanian J Med Dental Educ. 2020;9(6):62-68.
62. Klebanoff SJ. Myeloperoxidase: friend and foe. J Leukoc Biol. 2005;77(5):598-625.
63. Van der Veen BS, de Winther MP, Heeringa P. Myeloperoxidase: molecular mechanisms of action and their relevance to human health and disease. Antioxid Redox Signal. 2009;11(11):2899-2937.
64. Buchmann R, Hasilik A, Van Dyke TE, Lange DE. Amplified crevicular leukocyte activity in aggressive periodontal disease. J Dent Res. 2002;81(10):716-721.
65. Weiss SJ, Peppin G, Ortiz X, Ragsdale C, Test ST. Oxidative autoactivation of latent collagenase by human neutrophils. Science. 1985;227(4688):747-749.
66. Emingil G, Atilla G, Sorsa T, Tervahartiala T. Effects of sub-antimicrobial dose doxycycline therapy on crevicular fluid MMP-8, and gingival tissue MMP-9, TIMP-1 and IL-6 levels in chronic periodontitis. J Periodontal Res. 2004;39(3):206-215.
67. Lombardo G, Signoretto C, Corrocher G, Pardo A, Pighi J, Rovera A, et al. Adjunctive effects of a sub-antimicrobial dose of doxycycline on clinical parameters and potential biomarkers of periodontal tissue catabolism. Dent J (Basel). 2019;7(1):9.
68. Golub LM, Payne JB, Reinhardt RA, Nieman G. Can systemic diseases co-induce (not just exacerbate) periodontitis? A mechanistic model. Periodontol 2000. 2006;41:207-220.
69. D'Aiuto F, Orlandi M, Gunsolley JC. Evidence that periodontal treatment improves biomarkers and CVD outcomes. J Clin Periodontol. 2013;40 Suppl 14:S85-S105.
70. Hajdari I, Konjhodzic-Prcic A, Gavric J, Tuna A. Clinical therapeutic effects of the application of doxycycline in the treatment of periodontal disease. Med Arch. 2016;70(1):27-30.
71. Luchian I, Goriuc A, Sandu D, Covasa M. The role of matrix metalloproteinases (MMP-8, MMP-9, MMP-13) in periodontal and peri-implant pathological processes. Int J Mol Sci. 2022;23(3):1806.
72. Sorsa T, Hernandez M, Leppilahti J, Munjal S, Netuschil L, Mäntylä P. Detection of gingival crevicular fluid MMP-8 levels with different laboratory and chair-side methods. Oral Dis. 2010;16(1):39-45.
73. Faramarzi M, Azimi S, Rouhani H, Mahmoodi S, Goudarzi S, Yousefy A. Effects of locally delivered doxycycline on periodontal clinical parameters and matrix metalloproteinase-8 levels. J Int Oral Health. 2016;8(7):781-786.
74. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Clin Periodontol. 2018;45 Suppl 20:S149-S161.
75. Ökte E, Ayna B. Staging and grading periodontal diseases: A comprehensive review. Sisli Etfal Hastan

Tip Bul. 2019;53(3):244-249.
76. Wang CW, McCauley LK. Osteoporosis and periodontitis. Curr Osteoporos Rep. 2016;14(6):284-291.
77. Suvan J, Leira Y, Moreno F, Graziani F, Derks J, Tomasi C. Subgingival instrumentation for treatment of periodontitis. A systematic review. J Clin Periodontol. 2020;47 Suppl 22:155-175.
78. Preshaw PM. Host modulation therapy with anti-inflammatory agents. Periodontol 2000. 2018;76(1):131-149.
79. Alkan İİ, Yüzbaşioğlu E, Sağlam M, Paksoy T, Keskin F, Köseoglu S. The effectiveness of scaling and root planing with combined application of air polishing and Nd:YAG laser in the treatment of stage III grade C periodontitis. Clin Oral Investig. 2022;26(8):5341-5352.
80. National Library of Medicine (US). Three-session non-surgical periodontal therapy in stage III/IV grade C periodontitis. ClinicalTrials.gov Identifier: NCT07272980. Available at: https://clinicaltrials.gov/study/NCT07272980
81. Payne JB, Golub LM, Stoner JA, et al. The effect of subantimicrobial-dose-doxycycline periodontal therapy on serum biomarkers of systemic inflammation: a randomized, double-masked, placebo-controlled clinical trial. J Am Dent Assoc. 2011;142(3):262-273.
82. Preshaw PM, Hefti AF, Jepsen S, Etienne D, Walker C, Bradshaw MH. Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis. A review. J Clin Periodontol. 2004;31(9):697-707.
83. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers. 2017;3:17038.
84. Sorsa T, Gieselmann D, Arweiler NB, Hernández M. A quantitative point-of-care test for periodontal and peri-implant diseases. Nat Rev Dis Primers. 2017;3:17069.
85. Walker C, Thomas J, Nangó S, Lennon J, Wetzel J, Powala C. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. J Periodontol. 2000;71(9):1465-1471.
86. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. J Am Acad Dermatol. 2006;54(2):258-265.
87. Thomas J, Walker C, Bradshaw M. Long-term use of subantimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. J Periodontol. 2000;71(9):1472-1483.
88. Holmes NE, Charles PG. Safety and efficacy review of doxycycline. Clin Med Insights Ther. 2009;1:CMT.S2035.
89. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother. 2006;58(2):256-265.
90. [ffcoat MK, Page RC, Reddy MS, et al. Use of digital radography to demonstrate the potential of naproxen as an adjunct in the treatment of rapidly progressive periodontitis. J Periodontal Res. 1991;26(5):415-421.
91. Preshaw PM. Host response modulation in periodontics. Periodontol 2000. 2008;48:92-110.
92. [VanDyke TE, Sima C. Understanding resolution of inflammation in periodontal diseases: is chronic inflammatory periodontitis a failure to resolve? Periodontol 2000. 2020;82(1):205-213.
93. Carlucci AR, Szlapinski SK, Realini LRA, et al. Effects of host modulation through omega-3 dietary supplementation in periodontal treatment on inflammatory outcomes in humans: a scoping review. Einstein (Sao Paulo). 2024;22:eRW0509.
94. Pradeep AR, Thorat MS. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial. J Periodontol. 2010;81(2):214-222.
95. Herrera D, Sanz M, Jepsen S, Needleman I, Roldán S. A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients. J Clin Periodontol. 2002;29 Suppl 3:136-159.
96. Slots J. Selection of antimicrobial agents in periodontal therapy. J Periodontal Res. 2002;37(5):389-398.
97. Gomes SC, Piccinin FB, Oppermann RV, Susin C, Nonnenmacher CI, Mutters R, Marcantonio RA. Periodontal status in smokers and never-smokers: clinical findings and real-time polymerase chain reaction quantification of putative periodontal pathogens. J Periodontol. 2006;77(9):1483-1490.
98. Zhang Z, Li X, Liu Y, et al. Systemic doxycycline as an adjunct to nonsurgical periodontal therapy in diabetic patients with periodontitis: a systematic review and meta-analysis. Front Physiol. 2025;15:1479152.
99. Joshi D, Garg T, Goyal AK, Rath G. Advanced drug delivery approaches against periodontitis. Drug Deliv. 2016;23(2):363-377.
100. Bonito AJ, Lux L, Lohr KN. Impact of local adjuncts

to scaling and root planing in periodontal disease therapy: a systematic review. J Periodontol. 2005;76(8):1227-1236.
101. Faramarzi M, Azimi S, Rouhani H, Mahmoodi S, Goudarzi S, Yousefy A. Effects of locally delivered doxycycline on periodontal clinical parameters and matrix metalloproteinase-8 levels. J Int Oral Health. 2016;8(7):781-786.
102. Kinane DF, Radvar M. A six-month comparison of three periodontal local antimicrobial therapies in persistent periodontal pockets. J Periodontol. 1999;70(1):1-7.
103. Loos BG, Papantonopoulos G, Jepsen S, Laine ML. What is the contribution of genetics to periodontal risk? Dent Clin North Am. 2015;59(4):761-780.
104. Sorsa T, Gursoy UK, Nwhator S, et al. Analysis of matrix metalloproteinases, especially MMP-8, in gingival creviclular fluid, mouthrinse and saliva for monitoring periodontal diseases. Periodontol 2000. 2016;70(1):142-163.
105. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89(Suppl 1):S173-S182.
106. Needleman I, Garcia R, Gkranias N, et al. Mean annual attachment, bone level, and tooth loss: A systematic review. J Periodontol. 2018;89 Suppl 1:S120-S139.
107. Van Dyke TE, Sima C. Understanding resolution of inflammation in periodontal diseases: is chronic inflammatory periodontitis a failure to resolve? Periodontol 2000. 2020;82(1):205-213.
108. Sculean A, Nikolidakis D, Nikou G, Ivanovic A, Chapple IL, Stavropoulos A. Biomaterials for promoting periodontal regeneration in human intrabony defects: a systematic review. Periodontol 2000. 2015;68(1):182-216.
109. Giannobile WV. Salivary diagnostics for periodontal diseases. J Am Dent Assoc. 2012;143(10 Suppl):6S-11S.
110. Sorsa T, Gieselmann D, Arweiler NB, Hernández M. A quantitative point-of-care test for periodontal and peri-implant diseases. Nat Rev Dis Primers. 2017;3:17069.
111. Buduneli N, Kinane DF. Host-derived diagnostic markers related to soft tissue destruction and bone degradation in periodontitis. J Clin Periodontol. 2011;38 Suppl 11:85-105.
112. Tonetti MS, Chapple IL, Jepsen S, Sanz M. Primary and secondary prevention of periodontal and peri-implant diseases: Introduction to, and objectives of the 11th European Workshop on Periodontology consensus conference. J Clin Periodontol. 2015;42 Suppl 16:S1-4.
113. Needleman I, McGrath C, Floyd P, Biddle A. Impact of oral health on the life quality of periodontal patients. J Clin Periodontol. 2004;31(6):454-457.
114. Golub LM, Lee HM, Ryan ME, et al. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. Adv Dent Res. 1998;12(2):12-26.
115. Hernández M, Dutzan N, García-Sesnich J, et al. Host-pathogen interactions in progressive chronic periodontitis. J Dent Res. 2011;90(10):1164-1170