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# Host-modulatory therapy in periodontitis: Role of subantimicrobial-dose doxycycline and beyond

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## Abstract

Periodontitis is a chronic inflammatory disease in which tissue destruction results largely from an exaggerated host immune response to bacterial biofilms. Host-modulatory therapy (HMT) aims to control this destructive response and improve periodontal treatment outcomes. Among the various agents investigated, subantimicrobial-dose doxycycline (SDD) is the first and currently the only FDA-approved host-modulating drug used as an adjunct to conventional periodontal therapy. At low doses, doxycycline inhibits matrix metalloproteinases and reduces inflammatory mediators without exerting clinically significant antimicrobial effects. Clinical studies have demonstrated improved probing depth reduction and clinical attachment gain when SDD is used alongside scaling and root planing. Other host-modulatory approaches, such as non-steroidal anti-inflammatory drugs, bisphosphonates, specialised pro-resolving mediators, and chemically modified tetracyclines, have also been explored with varying levels of evidence. Although many of these agents show promising anti-inflammatory and bone-preserving effects, their routine clinical use remains limited. Host-modulatory therapy, therefore, represents an important adjunctive strategy in the comprehensive management of periodontitis.

**Keywords:** Host modulation therapy; Periodontitis; Subantimicrobial-dose doxycycline; Resolvins; Bisphosphonates; Matrix metalloproteinases

## 1. Introduction

Periodontitis is a chronic inflammatory disease driven by bacterial plaque biofilms, but the tissue destruction in periodontitis is largely a result of the host's immune-inflammatory response to the bacteria(1). Recognition of the host response as a key determinant of periodontal destruction has led to the concept of host-modulatory therapy: therapeutic strategies aimed at reducing or modulating the host's destructive immune response to slow periodontal breakdown and promote healing(2). The concept of host modulation in periodontitis was introduced in the early 1990s (notably by Williams and Golub) as a paradigm shift beyond traditional antimicrobial approaches(3,4).

Subantimicrobial-dose doxycycline (SDD) was the first HMT agent approved for periodontal treatment, targeting the host's enzymes rather than bacteria(5). Since then, a range of other host-modulating agents have been investigated, including anti-inflammatory drugs, bone-sparing medications, and emerging biologics, to manage periodontitis adjunctively(6). This review provides a comprehensive overview of HMT in periodontitis, with a particular focus on SDD's mechanism, pharmacology and clinical evidence, and examines the efficacy of other host-modulatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, specialised pro-resolving mediators (resolvins), and novel molecules.

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### 1.1. Subantimicrobial-Dose Doxycycline (SDD)

SDD refers to dosing of doxycycline at levels below the antimicrobial threshold (typically 20 mg twice daily). At this sub-antimicrobial dose, doxycycline does not exert clinically significant antimicrobial effects but retains the ability to inhibit host-derived MMPs that drive collagen breakdown(3,7). Notably, Golub and colleagues discovered that tetracyclines have this anti-collagenase property independent of their antimicrobial activity. By down-regulating excessive MMP activity, SDD aims to reduce the connective tissue destruction and bone resorption associated with periodontitis(8,9). Doxycycline at 20 mg b.i.d. is well below the antimicrobial MIC for periodontal pathogens, thus minimising the risk of disrupting the normal microbiota or inducing antibiotic resistance(10). Indeed, long-term SDD use (6–9 months or more) has not been associated with significant shifts in subgingival flora or emergence of resistant organisms in periodontal or gut flora. It is typically prescribed as an adjunct for at least 3 months and often up to 9 months or more, since its effects on the chronic inflammatory process require sustained dosing(11). Common doxycycline-related side effects (e.g. gastrointestinal upset, photosensitivity) are generally mild with SDD due to the low dose, and SDD is considered safe for long-term use in adults(12).

SDD was approved by the U.S. FDA in 1998 as an adjunct to scaling and root planing (SRP) for treating chronic periodontitis(13). In a pivotal 9-month multi-centre trial, adjunctive SDD (20 mg twice daily) led to greater reductions in probing depth (PD) and gains in clinical attachment level (CAL) compared to placebo(14). Biomarker studies reinforce SDD's mechanism: patients on SDD exhibit decreased collagenase (MMP-8 and MMP-9) levels in gingival crevicular fluid and reduced markers of bone resorption(15). These biochemical changes correlate with the clinical stabilisation of periodontal attachment. SDD's efficacy extends to various scenarios, and it has improved outcomes after periodontal surgery and has shown adjunctive benefits in diabetic periodontitis and in smokers, populations with heightened inflammatory responses(16). Beyond the oral cavity, the systemic anti-inflammatory action of long-term low-dose doxycycline has been noted to benefit certain comorbid conditions, highlighting how modulating MMPs and cytokines can have broad therapeutic implications(17).

### 1.2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

In periodontitis, prostaglandins, especially $PGE_2$, produced via the arachidonic acid/COX pathway, are important mediators that enhance inflammation and drive alveolar bone resorption(18). NSAIDs inhibit cyclooxygenase (both COX-1 and COX-2 isoforms), thereby reducing the synthesis of $PGE_2$ and other prostanoids. By blocking this pathway, NSAIDs can theoretically attenuate the inflammatory cascade that leads to connective tissue breakdown and osteoclast-mediated bone loss(19,20). Classic NSAIDs like flurbiprofen, naproxen, and indomethacin were among the first agents studied for host modulation in periodontitis, aiming to slow disease progression by interfering with prostaglandin-driven bone destruction. More selective COX-2 inhibitors (e.g. celecoxib) have also been explored to provide anti-inflammatory benefits with fewer gastrointestinal side effects, although concerns about cardiovascular risk exist for long-term use(21).

NSAIDs have been shown to reduce the rate of alveolar bone loss in experimental and clinical studies. In early landmark studies, Williams et al. showed that systemic flurbiprofen could significantly slow alveolar bone loss in periodontitis patients over long observation periods(22).

However, results from clinical trials have not been uniformly positive, especially for short-duration NSAID use. Haffajee et al. found that a 1-month regimen of systemic ibuprofen (400 mg three times daily) during active periodontal therapy did not significantly improve probing depth or attachment outcomes compared to placebo(23). In that study, only adjunctive antibiotics showed additional benefit. These short-term studies suggest that NSAIDs likely need to be administered for a longer duration to manifest meaningful effects on the chronic disease process(24). Notably, a large 12-month RCT by Yen et al. examined celecoxib (a COX-2 inhibitor) as an adjunct in chronic periodontitis. Patients who took celecoxib daily for one year in addition to SRP had greater pocket depth reduction and clinical attachment gains than those on SRP + placebo, particularly at sites with initially moderate-to-deep pockets. Celecoxib-treated patients also showed fewer sites with progressive attachment loss and improved bleeding scores(25).

On the other hand, topical NSAID applications have produced mixed results. For instance, a 1% flurbiprofen gel dentifrice used twice daily for 12 months did not significantly enhance probing depth reduction relative to a placebo paste. The variability in outcomes likely reflects differences in drug, dose, duration, and delivery method. Overall, the consensus is that systemic NSAIDs can inhibit periodontal disease activity (especially bone loss) when taken consistently over an extended period, but continuous long-term use is generally not feasible due to safety concerns(26).

Long-term use of non-selective NSAIDs can cause gastrointestinal ulceration, bleeding, and renal impairment, which outweigh the modest periodontal benefits for most patients. Even COX-2 selective drugs, while gentler on the GI tract,

carry risks of cardiovascular events with prolonged use(27). Moreover, when NSAID therapy is discontinued, the periodontal disease process can "rebound". Studies noted that bone loss resumes at rates similar to controls once the drug is stopped, meaning the benefit is not permanent. These factors make continuous NSAID therapy for periodontal patients inadvisable in routine practice(28). Instead, NSAIDs have been evaluated mostly as a temporary adjunct. To date, no NSAID is officially approved specifically for periodontal disease modification. Thus, while NSAIDs provided critical proof that modulating inflammatory mediators can alter periodontitis outcomes, their use in periodontal therapy remains off-label and is approached with caution(21).

## 2. Bisphosphonates

Bisphosphonates (BPs) are medications classically used to inhibit bone resorption in diseases like osteoporosis, Paget's disease, and skeletal metastases. They are analogues of pyrophosphate that have a high affinity for bone mineral (hydroxyapatite) and specifically disrupt osteoclast-mediated bone resorption(29). Bisphosphonates also can have anabolic or protective effects on bone: they have been shown to increase osteoblast differentiation and activity, and to reduce the formation of new active remodelling units, tipping the balance toward bone retention. In essence, BPs help preserve bone mass(30). In the context of periodontitis, where alveolar bone loss is a hallmark of disease progression, there is a clear rationale to repurpose bisphosphonates as host-modulating agents to slow or prevent periodontal bone resorption. Interestingly, some bisphosphonates may also inhibit MMPs in vitro, adding a potential anti-collagenase effect to their anti-resorptive action(31).

Animal studies provided initial proof of concept that bisphosphonates could mitigate periodontal bone loss. Shoji et al. (1995) demonstrated that systemic BP administration in a rat periodontitis model significantly prevented alveolar bone resorption compared to controls. These encouraging results led to human trials(32). One of the seminal clinical studies was a 12-month randomised controlled trial by Lane et al. (2005), which evaluated systemic bisphosphonate therapy as an adjunct to SRP in patients with moderate to severe periodontitis. Over the course of a year, the BP-treated group (who received daily oral bisphosphonate in addition to SRP and maintenance care) showed significantly better clinical outcomes than the placebo group – including greater gains in clinical attachment level, reduced pocket depths, and less bleeding on probing. Although radiographic bone mass changes in that study did not reach statistical significance in favour of BPs, the trends suggested a stabilisation of bone levels(33).

Researchers have tested bisphosphonates in various modes: systemically (e.g. weekly or daily oral alendronate) and locally (such as bisphosphonate gels or ointments applied into periodontal pockets or onto root surfaces during surgery)(34). Topical application is particularly attractive to avoid systemic side effects. Notably, studies using locally delivered alendronate (often in intrabony defects or following periodontal surgery) reported greater defect fill and bone regeneration in the BP-treated sites versus controls. Despite their efficacy in preserving bone, the use of bisphosphonates in periodontics must be weighed against potential risks. The most serious is osteonecrosis of the jaw (ONJ), a condition of non-healing jaw bone exposure, which has been associated with high-dose or long-term bisphosphonate therapy (especially intravenous BPs in cancer patients). While the doses used for osteoporosis (or in short-term periodontal trials) are much lower risk, the theoretical possibility of ONJ, particularly if invasive dental procedures are needed, raises concern(35). In the 2023 systematic review, the authors concluded that although adjunctive BP therapy appears effective for periodontitis, its practical applicability is questionable given the risk of ONJ and the relatively short follow-ups available so far. No cases of ONJ were reported in the periodontitis trials to date, but typically, those studies limited BP exposure to ~6–12 months(36). Another limitation is that bisphosphonates, when used systemically, affect the entire skeleton, which is beneficial for patients who also have osteoporosis, but it means one would be treating beyond the target of the periodontal tissues, with possible systemic side effects (e.g. altering bone turnover in other sites, potential for hypocalcemia, etc.)(37).

Thus, local delivery strategies are being investigated as a safer approach in the periodontal context. Topical bisphosphonate application confines the drug to the periodontium and has shown promising localised bone retention without systemic exposure. Still, local therapy might be impractical for generalised periodontitis (it would be more feasible in isolated defects during surgery). At present, no bisphosphonate is officially approved for periodontal therapy. Their use remains experimental or off-label, and would typically be reserved for select cases at high risk of rapid bone loss. Careful patient selection (avoiding those with comorbid conditions or medications that compound ONJ risk) and limited-duration regimens are prudent if BPs are employed(38).

## 3. Specialised Pro-Resolving Mediators (Resolvins and Related Molecules)

The inflammatory response normally has two phases, namely initiation and resolution. In periodontitis, a failure of active resolution mechanisms contributes to a chronic, non-resolving inflammation that perpetuates tissue destruction. Specialised pro-resolving mediators (SPMs) are a group of endogenous lipid-derived compounds that actively orchestrate the resolution of inflammation. These mediators are biosynthesised from ω-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), or in the case of lipoxins, from arachidonic acid via transcellular biosynthesis. Key SPMs in periodontitis research are Resolvin E1 (RvE1) (derived from EPA) and lipoxin A4 (derived from arachidonic acid), among others(39).

RvE1 is the most extensively studied SPM in periodontitis contexts. In a study, Hasturk et al. applied RvE1 to treat experimental periodontitis in rabbits. They reported that promotion of resolution with RvE1 led to near complete regeneration of the periodontal tissues destroyed by disease, including regeneration of lost alveolar bone, effectively restoring the periodontium to a healthy state(40). This remarkable finding (the first demonstration of complete natural regeneration via a chemical mediator) highlighted RvE1's potent actions: it locally stopped leukocyte recruitment and countered the tissue-destructive effects of prostaglandin $E_2$ and leukotriene $B_4$, which conversely were shown to worsen the disease. In RvE1-treated sites, not only was inflammation resolved, but bone levels returned to baseline, and systemic inflammatory markers (like C-reactive protein and IL-1β) were reduced. Follow-up studies in a rat ligature-induced periodontitis model confirmed that topical RvE1 application can prevent and reverse periodontal tissue breakdown, with regeneration of soft and hard tissues back to near pre-disease conditions(41).

Mechanistically, resolvins operate through specific receptors on target cells. It can inhibit neutrophil chemotaxis and also "reprogram" macrophages toward a pro-resolving phenotype that secretes anti-inflammatory cytokines (IL-10, TGF-β) and growth factors for tissue repair(42). Crucially for periodontitis, RvE1 has direct effects on bone cells: it binds BLT1 on osteoclast precursors to suppress RANKL-stimulated osteoclast differentiation, and it binds ChemR23 on osteoblasts to stimulate production of osteoprotegerin (OPG), the decoy receptor that inhibits osteoclast activation. Through these dual actions, RvE1 both inhibits bone resorption and potentially promotes bone formation. Indeed, in animal models, RvE1-treated sites showed fewer osteoclasts and signs of bone regeneration alongside resolution of inflammation(43).

Another interesting observation is that effective resolution of inflammation by RvE1 can beneficially alter the local microbial ecosystem. In the rat model, RvE1 treatment led to normalisation of the plaque biofilm after the acute insult: as inflammation resolved, the proportions of periodontopathogens like *P. gingivalis, A. actinomycetemcomitans,* and *F. nucleatum* decreased, and the microbiota shifted back towards a healthy composition(44). This supports the "ecological plaque hypothesis", reducing inflammation can create a microenvironment less favourable to pathogenic bacteria. Thus, host modulation with resolvins might indirectly help control dysbiosis, complementing mechanical cleaning and antimicrobial measures(45).

Besides RvE1, other SPMs and analogues have shown promise in preclinical studies of periodontitis. Lipoxin A4 (LXA4), an endogenous arachidonic acid-derived resolvent, has been studied in transgenic mice and rabbit models: it can curb neutrophil recruitment and IL-1β levels, protecting against periodontal bone loss. An analogue of LXA4 applied with guided tissue regeneration was reported to improve outcomes in dog periodontal defects, suggesting a potential regenerative adjunct(46). Maresins and protectins (from DHA) likewise have potent anti-inflammatory effects, though specific studies in periodontitis are limited. In general, pro-resolving therapy is an active area of research; efforts are underway to develop stable analogues of resolvins/lipoxins that could be used as drugs (natural SPMs are quickly metabolised). One notable strategy in humans has been dietary supplementation with omega-3 fatty acids to boost the body's substrate for SPM production, often combined with low-dose aspirin (aspirin triggers the formation of epimeric SPMs like aspirin-triggered resolvins and lipoxins). In a clinical study, patients given omega-3 PUFA (EPA+DHA) supplements plus 81 mg aspirin daily showed significantly greater reductions in pocket depth and improved attachment levels over 6 months, compared to controls on periodontal therapy alone. These benefits are attributed to increased endogenous resolvin/lipoxin generation. Such findings illustrate a translational path for pro-resolving mediators in managing periodontitis(47).

## 4. Chemically Modified Tetracyclines (CMTs)

These are derivatives of tetracyclines that have been chemically altered to remove antimicrobial activity while preserving MMP-inhibitory properties. One example is CMT-3 (COL-3), a modified minocycline. Golub et al. pioneered this idea, demonstrating that a 4-dedimethylaminotetracycline could inhibit collagenase without antibiotic effects.

CMTs showed efficacy in animal models of periodontitis similar to SDD, reducing connective tissue loss(9). Despite promising data, CMTs have not become commercially available for dentistry, partly due to the success of SDD. Nonetheless, they represent an interesting class of host modulators and could see renewed interest for patients where antibiotic exposure must be absolutely avoided(8).

Though primarily aimed at modulating the microbiome, probiotics also interact with the host immune system and can be considered a host-modulatory approach. Certain probiotic strains have been shown to alter cytokine profiles and reduce inflammatory markers in the oral cavity. Clinical trials of probiotic lozenges or supplements in periodontitis have noted improvements in gingival inflammation and plaque indices(48).

Ongoing periodontal research is investigating various new drugs targeting host pathways. For example, matrix metalloproteinase inhibitors beyond tetracyclines were developed in other fields; agents like periostat (SDD) remain unique in dentistry due to safety, but newer MMP inhibitors or aggrecanase inhibitors could be repurposed if they overcome systemic toxicity. Anti-protease therapies have been tested for osteoporosis (odanacatib) and could theoretically help in periodontitis by reducing bone resorption, though odanacatib's development halted due to side effects(6,49). Table 1 summarizes the host modulatory agents used in periodontal therapy.

**Table 1** Host-modulatory agents in periodontal therapy

| Agent/Class | Mechanism of Action | Delivery | Clinical Evidence |
|---|---|---|---|
| Subantimicrobial-Dose Doxycycline (SDD) | MMP inhibition | Systemic (oral, 20mg b.i.d.) | Strong evidence, FDA approved |
| NSAIDs | Inhibits COX enzymes, reduces PGE2 and inflammation | Systemic or topical | Mixed; long-term use is limited by side effects |
| Bisphosphonates | Inhibits osteoclast-mediated bone resorption | Systemic or local (gels, graft coatings) | Good evidence; limited by ONJ risk |
| Resolvins (RvE1, LXA4) | Promotes resolution of inflammation, tissue regeneration | Local (topical) or dietary (ω-3 fatty acids) | Strong preclinical, limited human data |
| Cytokine Inhibitors | Block IL-1/TNF | Systemic (injections) or potential local gels | Experimental, limited to systemic disease |
| Probiotics | Modulates the immune response and oral microbiota | Oral (lozenges, supplements) | Supportive evidence in inflammation control |
| Statins (Local Application) | Promotes bone formation, anti-inflammatory | Local (gels, pastes) | Promising early evidence |

## 5. Discussion

Host-modulatory therapy has emerged as an important adjunctive strategy to improve periodontal treatment outcomes. The clinical implications of incorporating HMT alongside conventional scaling and root planing are significant(50). By targeting the inflammatory mediators and destructive enzymes of the host, these therapies can help stabilise periodontal status in ways that mechanical debridement alone might not achieve(51). Thus, SDD is often used during periodontal maintenance phases to slow disease progression. Other agents like NSAIDs and bisphosphonates, while not part of routine care, have demonstrated that specific clinical scenarios might benefit from host modulation(52). Bisphosphonate adjunctive therapy might be considered in osteoporotic patients with periodontitis, potentially addressing two conditions at once, though careful coordination with physicians is required(53).

Another clinical implication is in the realm of periodontal-systemic health connections. By modulating the periodontal inflammation, HMT might also reduce the systemic inflammatory burden(54). Despite the promise of host-modulatory therapy, several limitations temper its use. Safety and side effects are the foremost concern. Periodontitis is a chronic disease, often requiring lifelong management, so any systemic medication given as an adjunct may need to be taken for months or years(55). This heightens the importance of a favourable safety profile. NSAIDs, as discussed, carry the risk of peptic ulcers, kidney injury, and cardiovascular events, making them unsuitable for long-term preventive therapy in periodontitis(56). Bisphosphonates, while generally safe in osteoporotic doses, raise the spectre of jaw osteonecrosis,

particularly if surgical periodontal treatment is performed in a patient on BP therapy(57). Even the theoretical risk of ONJ has made clinicians very cautious about using BPs purely for periodontitis. Any patient on adjunctive BPs would need informed consent and co-management with their physician, and invasive dental procedures should be minimised or done with drug holidays if possible(58).

For the newer agents like resolvins or cytokine inhibitors, one limitation is the lack of long-term human data. Their safety profiles are not fully characterised in the context of periodontal use. Biologics could increase infection susceptibility if used broadly(59). Pro-resolving lipid mediators might have fewer obvious side effects, but large-scale trials are needed to ensure they do not, for example, overly suppress necessary inflammation or have unexpected effects on coagulation, etc. Additionally, many of these agents are not yet approved or available for dental use(42,60). SDD is currently the only FDA-approved systemic host modulatory drug for periodontitis. NSAIDs and others would be off-label usage. Resolvins are still investigational. Regulatory approval requires demonstrating a favourable risk-benefit ratio specifically for periodontal indications, which can be a high bar for drugs that may have systemic actions(61).

Another practical limitation is patient adherence and cost. Taking a pill every day for periodontal disease is a commitment; studies find that compliance can wane over time, especially if patients do not perceive immediate benefits. The cost of medications could be prohibitive if not covered by insurance for this indication(62).

### *Future Directions*

The field of host modulation in periodontitis is dynamic and holds exciting prospects. Future research is likely to focus on refining existing therapies and discovering novel targets. A major direction is improving local delivery systems for host modulators to maximise periodontal benefits while minimising systemic exposure. For MMP inhibitors like doxycycline, formulations such as subgingival slow-release or injectable systems could be explored to supplement systemic dosing(63,64).

There is also interest in whether combining host agents could have synergistic effects, for instance, SDD + NSAID together. One study found that a sub-antimicrobial dose of doxycycline combined with a low-dose flurbiprofen had additive effects on reducing GCF MMP levels compared to either alone(65).

## 6. Conclusion

Host-modulatory therapy has moved periodontitis treatment into a new era where we are not only fighting bacteria but also modulating the body's response. SDD has established the viability of this approach, and "beyond SDD," an array of agents is on the horizon that could further transform periodontal management. While challenges around safety and patient selection remain, the continued integration of dental and medical research will likely yield innovative solutions. Ultimately, a multi-pronged strategy addressing both infection control and host response offers the best hope for managing periodontitis, especially in susceptible individuals.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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