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A Comprehensive Review on SDD and its Role in Host Modulation

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ABSTRACT

Periodontitis is a serious gum infection characterized by inflammation, followed by the destruction of the supporting structures of the tooth, including bone loss. Etiology of Periodontal disease is multifactorial which involves the role of host immunoinflammatory response and bacterial virulence factors. Host modulation therapy aims at downregulating or altering the destructive aspects of host response. Subantimicrobial Dose Doxycycline (SDD) is one such host modulatory agent that exerts its effects primarily through the inhibition of matrix metalloproteinases (MMPs) enzymes responsible for the degradation of extracellular matrix components, such as collagen, within the periodontal tissues. SDD is given as an adjunct to scaling and root planning. The present review focuses on SDD, its mechanism of action and application in host modulation therapy.

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Introduction

Chronic periodontitis is a progressive inflammatory disease characterized by the destruction of the supporting structures of the teeth, including the periodontal ligament and alveolar bone. The etiology is multifactorial, involving a complex interplay between pathogenic bacteria and the host's immune-inflammatory response, influenced by environmental and genetic factors. Traditionally, the management of chronic periodontitis has focused on mechanical debridement through scaling and root planing (SRP), aimed at reducing the microbial load. However, mechanical therapy alone may not adequately control the host-mediated tissue destruction that continues even after bacterial reduction.

Advancements in periodontal therapy emphasize the importance of modulating the host response in conjunction with traditional mechanical approaches. This shift has led to the exploration of adjunctive therapies targeting the biochemical pathways involved in tissue degradation.

The concept of HMT was introduced in dentistry by "Williams and golub" et al. [1].

Subantimicrobial Dose Doxycycline

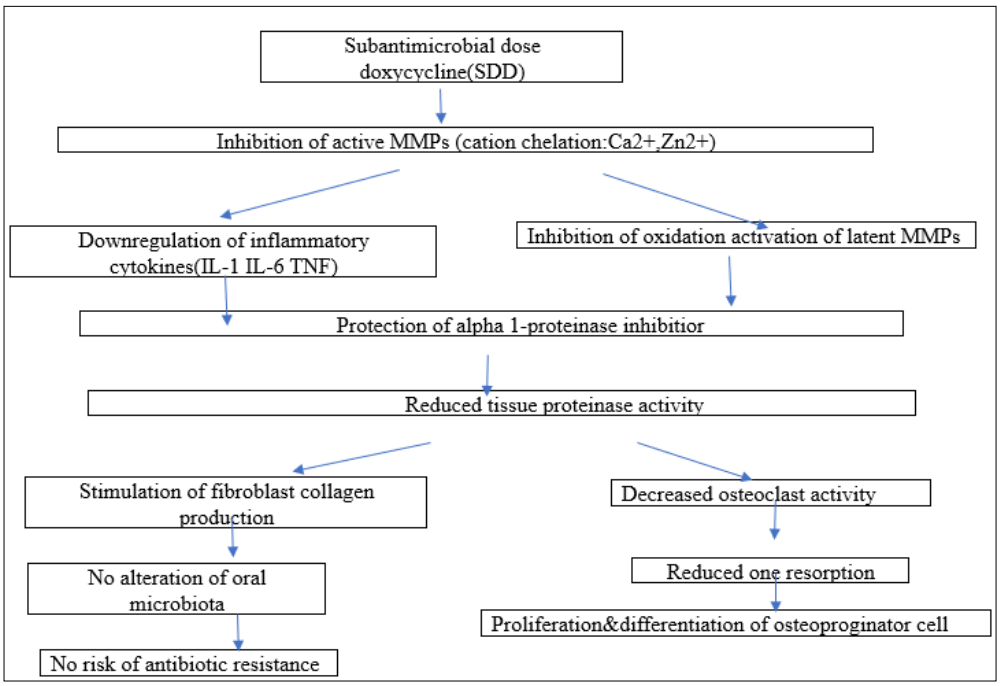
Subantimicrobial Dose Doxycycline (SDD), an FDA-approved formulation of doxycycline (20 mg), known commercially as Periostat [1]. Unlike conventional antibiotic doses, SDD exerts its effects primarily through the inhibition of Matrix Metalloproteinases (MMPs)—enzymes responsible for the degradation of extracellular matrix components, such as collagen, within the periodontal tissues.

Mechanism of Action

SDD involves taking doxycycline at a low dose (20 mg twice daily), which is below the typical antimicrobial threshold [2-5].

- I**nhibition of Active MMPs:** Doxycycline chelates metal ions like calcium (Ca^{2+}) and zinc (Zn^{2+}), essential for the activity of matrix metalloproteinases (MMPs). This chelation inhibits the enzymatic activity of MMPs directly, reducing their ability to degrade collagen in the periodontal tissues.
- **Inhibition of Oxidative Activation of Latent MMPs:** SDD prevents the conversion of inactive (latent) MMPs into their active form by inhibiting oxidative processes, which are usually mediated by reactive oxygen species (ROS).
- **Down regulation of Inflammatory Cytokines:** SDD reduces the expression of key inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which play a significant role in the inflammatory response and tissue destruction in periodontitis.
- **Reduction of Prostaglandin E2 (PGE2) Levels:** SDD decreases the levels of PGE2, a pro-inflammatory mediator associated with bone resorption and increased inflammation in periodontal disease.
- **Scavenging Reactive Oxygen Species (ROS):** By neutralizing ROS produced by neutrophils, SDD reduces oxidative stress in periodontal tissues, helping protect against further tissue damage.
- **Protection of α1-Proteinase Inhibitor:** By reducing oxidative stress, SDD protects α1-proteinase inhibitor, which prevents excessive tissue proteinase activity and subsequent tissue degradation.
- **Reduction of Tissue Proteinase Activity:** With decreased MMP activity and protected α1-proteinase inhibitor, the overall proteinase activity in periodontal tissues is reduced, slowing down the breakdown of connective tissue.

- **Stimulation of Fibroblast Collagen Production:** SDD promotes collagen synthesis by stimulating fibroblasts, enhancing tissue repair and stability in the periodontal environment.
- **Decrease in Osteoclast Activity and Bone Resorption:** SDD reduces osteoclast activity, leading to a decrease in bone resorption, which helps maintain bone levels in patients with periodontitis.
- **Enhancement of Osteoprogenitor Cell Proliferation:** SDD positively influences the proliferation and differentiation of osteoprogenitor cells, which are essential for bone regeneration and healing.
- **No Alteration of Oral Microbiota:** Unlike traditional antibiotic doses, SDD does not have significant antibacterial effects, preserving the normal oral microbiota.
- **Prevention of Antibiotic Resistance:** The low dose does not disrupt bacterial populations, thus minimizing the risk of developing antibiotic resistance, making it a safe long-term adjunctive therapy.



Combination Therapy with SDD

The efficacy of scaling and root planing in patients with adult periodontitis by J G Caton et al have shown that SDD, when prescribed as an adjunct to scaling and root planing, results in statistically and clinically significant gains in attachment level and reductions in probing depth over and above those that are achieved by scaling and root planing alone. SRP must be thorough to maximize the benefit of adjunct to SDD.SDD does not result in antibacterial effect, or lead to the development of resistance strains or the acquisition of multiantibiotic resistance [6].

Indication

- In the management of chronic periodontitis and aggressive periodontitis
- In patients with aggressive periodontitis who are being treated non surgically
- SDD as an adjunct to periodontal surgery
- Refractory to treatment
- Risk factors such as smoking or diabetes in whom the treatment response might be limited [7].

Contraindication

- Any patient with a history of allergy or hypersensitivity to tetracycline
- Pregnant or lactating women
- Children less than 12 years old because potential for discoloration of the developing dentition
- Doxycycline may reduce the efficacy of Oral contraceptives and other alternative forms of birth control
- There is a risk of increased sensitivity to sunlight seen with higher doses of doxycycline although this has not been reported in the clinical trial antimicrobial dose [7].

Clinical Guidelines for SDD Usage in Periodontics

Adjunct to Scaling and Root Planing (SRP)

SDD should be used as an adjunctive therapy alongside conventional mechanical debridement like SRP to enhance treatment outcomes by reducing inflammation and preventing further connective tissue breakdown.

Dosage and Duration

- The recommended dosage of SDD is doxycycline hyclate 20 mg, taken twice daily. The typical duration of therapy is 3-9 months, depending on the severity of the disease and patient response [8].
- Regular clinical evaluations should be conducted every 3 months to assess periodontal status and determine if continuation of therapy is necessary.

Monitoring and Follow-Up

- Periodic monitoring of periodontal parameters, such as probing pocket depths (PPD), clinical attachment level (CAL), and bleeding on probing (BOP), should be conducted to evaluate the effectiveness of the therapy.
- Continuous monitoring of potential side effects, such as gastrointestinal disturbances, is recommended.

Patient Education and Compliance

- Patients should be informed about the purpose of SDD therapy, emphasizing its role in host modulation rather than bacterial elimination.
- Educating patients on the importance of compliance with dosage and regular periodontal maintenance is crucial for the success of therapy.

Use in Conjunction with Other Therapies

SDD may be combined with other host-modulating therapies, such as omega-3 fatty acids or anti-inflammatory agents, for synergistic effects in reducing periodontal inflammation [9].

Risk Assessment

A comprehensive risk assessment, including evaluation of patient's lifestyle factors like smoking, stress, and oral hygiene practices, should be performed to customize SDD therapy and ensure the best clinical outcomes.

Dosage, Formulation and Administration

A Subantimicrobial Dose of Doxycycline (SDD) at 20 mg (Periostat®) has been found to be a safe and effective adjunct when taken twice daily for at least 3 months and up to 24 months in randomized placebo controlled clinical trials. Periostat® is currently the only FDA approved inhibitor of the matrix metalloproteinases implicated in the plaque-induced pathologic degradation of connective tissue collagen of the periodontal [10].

Conclusion

Adjunctive SDD confers clinical benefit to paients with periodntitis.A comprehensive treatment strategy is suggested, involving patient education and motivation,reduction of the bacterial burden by SRP, host response modulation wth SDD, and periodontal risk factor modification

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